# PILOT SURVEY OF HUMAN LUNG TISSUE FOR AIR POLLUTION EFFECTS IN LOS ANGELES COUNTY

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ABSTRACT

The lungs from youths 14 to 25yrs of age, who were killed in vehicular accidents or by homicide, were the central part of a feasibility demonstration study. The specific goals were to accession lungs at autopsy, test special pathologic methodologies, search for early lesions of destructive lung disease, and assess the availability of demographic and air pollution data. Feasibility was demonstrated for the pathologic study in that 107 of 117 lungs meeting the selection criteria were accessioned, processed, and analyzed. Methodologies successfully applied included a perfusion-inflation apparatus for multiple-lung and multiple-day fixation, image analysis for the quantitation of bronchial submucosal glands (mucus content and gland structure), and rotary electrical slicing for whole lung gross evaluation of disease in general and emphysema in particular. The emphysema methodology proved to be insufficiently sensitive for optimal detection and measurement, but we successfully substituted a sledge microtome-diazo replication technique. Lung elastin quantitation was not feasible with the available analyzer; a replacement analyzer with a true color detector is needed. The fluorescent antibody cell sorter for the quantitation of lymphocyte subpopulations (lung hilar nodes) achieved some degree of successful labeling, i.e. 59 of 67 cases (88%). The demographic study was limited by early complications in the letters of introduction, interview protocols, and interviewer assignments. Feasibility of next-of-kin interviews was in large part demonstrated at the end of the study period as new data sources were identified. However, only limited demographic data were obtained on 29 cases (1987-1989) randomly selected. Of the 29 cases, 11 next-of-kin individuals were contacted and of these 60% were successfully interviewed. A protocol for obtaining blood samples was effected and specimens from 30 cases have been made available for cotinine and cannabinoid tests.

Slight to moderate degrees of centriacinar region (CAR) chronic inflammation were found in 51 (48%), and the inflammation was severe and extensive in 29 (27%), with the 27 remainder having minimal or no inflammation (25%). Of the 29 with severe CAR disease, 14 were listed as residents of Los Angeles, 7 were from other cities in Los Angeles County, and the records immediately available (Case Reports) for 8 did not list residence. A definitive study of present and prior residences is a part of an ongoing demographic study. Chronic bronchitis was present in 112 of the 117, and did not parallel the extent and severity of CAR disease. These preliminary findings, when added to the general literature on the adverse effects of air pollution, indicate a strong potential for the use of human pathologic studies in the evaluation of community air quality.

## STATEMENT OF CONTRACT

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## SUMMARY AND CONCLUSIONS

### Scope of project

A pilot study of the lungs of 15-25 year old individuals was carried out using Medical Examiner cases of violent deaths. The purpose was to demonstrate the feasibility of applying pathologic and epidemiologic methodologies to a study that would attempt to correlate human lung lesions with adverse effects of community air pollution. The pathologic methodologies were aimed at developing protocols for the accessioning and processing of lungs from the Medical Examiner Office, and then identifying early lesions of lung disease that may be promoted or exacerbated by community air pollution. The epidemiologic study had as its principal goal the development of protocols for communicating with the next-of-kin of the deceased, and then deriving demographic data for potential use in pathologic-demographic correlations centering on the adverse health effects of air pollution. The rationale for the pathologic study is that all adults have some degree of lung disease (e.g. emphysema) and air pollution can be expected to play some role in the causation, promotion, facilitation, and/or exacerbation not only of the overt disease but the progression of early lesions. The basis for the epidemiologic study is the variability in levels of air pollution to be found in Los Angeles County and communities in general. The finding that air pollution has an influence on the rate at which human lung structure deteriorates would be significant for two principal reasons, an implied increase in susceptibility to disease in general through the loss of lung reserves and the greater likelihood of progression to clinically manifested lung disease such as emphysema.

### Feasibility of the Experimental Design and Methodologies

The first step in the feasibility demonstration was the testing of the protocol for acquiring and processing lungs. This phase was successful in the following respects: 1) the numbers and kinds of cases coming to autopsy satisfactorily met the needs of the study; 2) the principal methodologies proposed for processing the lungs were feasible, i.e. the perfusion-inflation apparatus for multiple lung fixation over 48 hour periods, rotary electrical slicing for gross tissue processing and gross disease evaluation, special stains for selectively identifying bronchial mucous glands and elastic fibers, and image analysis for mucous gland hypertrophy and atrophy; 3) a close working relationship was successfully developed with the Medical Examiner's Office and included joint authorship of reports based on consultations; 4) the reports to the Medical Examiner on gross descriptions of the lungs and the supplementary information afforded satisfied the needs of the final autopsy report; 5) the microscopic examination revealed a surpris-

ing number and severity of pathologic lesions, in particular Centriacinar Region (CAR) disease and Chronic Bronchitis; 6) the broad spectrum of component parts of the lesions that was found indicates a strong potential for use as discriminants for epidemiologic correlations. 7) a semi-quantitative measurement of CAR disease and chronic bronchitis was successfully applied in that the data obtained defined three groups, those individuals with no disease, mild to moderate disease, and severe disease; 8) certain technical aspects were shown to be feasible, in particular the procedure for handling hazardous lung tissues and the disposal of hazardous wastes; 9) the fluorescent antibody cell sorter quantitation of lymphocyte subpopulations was successful in that labeling and measurement of T lymphocyte subpopulations from hilar lymph nodes were achieved in 88% of of the cases. Natural killer cells (NK cells) were detected in 8% of cases;

Some methodologies were not successful. The proposed method for detecting emphysema (a rotary slicer sectioning of gelatin embedded lungs) was less sensitive than needed for the detection of early emphysematous disease in youths. However, we successfully substituted a highly sensitive, although more labor intensive, sledge microtome-diazo replication technique. The methodology for image analysis quantitiation of lung elastin content was not satisfactory with the monochrome detector available.

**Preliminary pathologic data**

The pathologic investigation identified and quantified "early" lesions of lung disease in teenagers and young adults. A total of 163 lungs were obtained from the Coroner's Office. Lungs from 118 cases were processed and examined, and 107 were found to be suitable for analysis. The outstanding finding was the presence of some degree of Centriacinar Region (CAR) disease, i.e. chronic inflammation of respiratory bronchioles and adjacent acinic structures that is ordinarily manifested as subclinical disease. CAR disease was severe in the lungs of 29 cases (27%), slight to moderate for 51 cases (48%), and minimal or not observed for 27 cases (25%). There were lesions other than CAR disease. Chronic bronchitis was present in the lungs of all cases where tissues were available for examination (112/117). In the majority of instances (62%) the inflammation within the submucosa was slight to moderate, there were 6 cases (6%) with severe inflammation and 35 cases (32%) of minimal or absent inflammation. The corresponding percentages for chronic inflammation involving the epithelial mucosal lining, as opposed to the underlying submucosal glands and periglandular tissue, were 12% severe, 64% slight to moderate, and 24% minimal or absent. CAR disease occurred with and without pigment deposits and/or phagocytosis by macrophages, suggesting multifactorial origin. Chronic bronchitis was present to some extent in the lungs of all cases. Both chronic bronchitis and chronic interstitial pneumonia were in part independent of CAR disease.

## Preliminary Results of Demographic Study

The demonstration of feasibility for the epidemiologic phase of the study was partially successful in that many of the obstacles encountered were largely overcome by the final period of the study. It was possible to achieve a workable cooperative arrangement with the two universities (UCLA and USC) and the Medical Examiner's Office. We reworked letters of introduction, demographic forms, and interview protocols for improved yield and official approvals. Contacting the next-of-kin was initially difficult. Of the 29 cases assigned to the definitive interviewer (earlier interviewers had not been successful), only 11 (38%) were successfully contacted and just 60% were successfully interviewed. Additional reworking of the protocols indicated that the yield would be substantially improved by attention to the more current cases and the use of newly identified sources of data, e.g. mortuary and property records of the MEC Office. A protocol for obtaining blood samples was effected and specimens from 30 cases have been made available for cotinine and cannabinoid tests. Toxicological tests for substances of abuse are a routine part of homicide and vehicular accident deaths, and the results remain to be collated. Of the 29 severe CAR disease cases, 14 had Los Angeles addresses, 7 were from other cities in Los Angeles County, and there were 8 cases where data were not immediately available. For the slight to moderate cases, and those with no observed CAR disease, the ratios of LA city to LA county residents were 1/3 (11/30) and 1/1.3 (11/14), respectively.

## Significance

The main conclusion is that the severity and extent of CAR disease in the youths was unexpectedly high (27%). The subpopulation appears to be biased by socioeconomic factors, including selection through violent death (homicide or vehicular accident) and resident listings dominated by a central Los Angeles location. However, the high prevalence of CAR disease, chronic bronchitis, and other lung lesions in young and ostensibly healthy individuals raises a concern about the health status of the cohorts of this subpopulation. Further, the fact that ambient levels of air pollution can produce a milder form of CAR disease suggests that adverse environmental effects are a part of a multifactorial pathogenesis. While the injury to the subpopulation studied may largely reflect exceptionally severe personal and environmental circumstances, some instances of severe disease may represent especially susceptible individuals. Further, the subpopulation may be a bellwether pointing to an adverse effect over the long term on the population as a whole. We emphasize that CAR disease attributable to smoking or ozone exposure alone is a relatively mild lesion, and that the interaction of many agents is most likely responsible for the lung

lesions observed. Lastly, the CAR injury associated with evidence of irreversible damage, e.g. fibrosis and structural derangement, raises the question of some functional and/or clinical manifestations.

The limitations of the immunologic findings preclude any conclusion other than the potential usefulness of postmortem material for in vitro measurements and analysis of lymphoid tissues and cell subpopulations.

## RECOMMENDATIONS

The pathologic study has demonstrated that accessioning and processing of lungs can be successfully accomplished by the protocol used in the feasibility study. However, a substantial increase in data is potentially available. We recommend the following:

1. Assignment of a part-time pathologist, full-time resident, or full-time post-doctoral fellow to the Medical Examiner's Office.

Some transplantation facilities have awarded funds to the Medical Examiner's Office to assist in tissue "harvesting". A major benefit is the immediate availability of a prosector and the consequent benefit of good tissue preservation through a very short postmortem interval time. Good tissue preservation would optimize image analysis quantitation of cells, secretory products, and connective tissues. In addition, short postmortem intervals increase the viability and membrane integrity of immune cells of the host defense system, thus facilitating immunologic investigations with monoclonal and/or polyclonal antibodies. Further, autopsies are often not done when the workload is excessive and the circumstances not demanding, e.g. vehicular accidents without criminal charges, and suicides. The availability of a pathologist specifically for the support of a donor program would greatly increase and thereby optimize the numbers of cases available. Funding could be shared by interested private and governmental agencies to cover the cost of the ancillary autopsy service. At this time, a private agency is supporting a senior and part-time pathologist for assistance to the Medical Examiner.

2. A member of the epidemiologic team should be closely associated with the lung accessioning process, including a review of records for eligibility of the case prior to accessioning, or when not possible, prior to lung examination at the earliest stage. The demographic data should be "blinded", for the most part, from the investigator responsible for the pathologic study.

3. Next-of-kin interviews should be conducted soon after the autopsy. Although the optimal time for interview has not been fully established, it is clear from the preliminary studies that a long delay diminishes the success rate. The selection of an interviewer with experience and with a strong commitment to the project are critical needs. During the study, sources of information with the potential of resolving many of the problems involved in next-of-kin interviews were identified and need to be exploited, in particular the mortuary section that is in contact with the undertakers. Telephone numbers and/or addresses are almost always readily available through the cooperation of the undertakers. Similarly, the property section is often in contact

with immediate relatives. Good public relations through the radio and television networks would add to the level of success in retrieving needed data. The questionaires and letters of introduction developed during the project appear to be satisfactory, but may merit some revision.

4. Expansion of the study into a multi-city project has the potential of sorting out the multiple factors that contribute to the various lung lesions found in the preliminary study. Sorting out the confounding factors would also be materially assisted by special tests of the CAR lesion for heavy metals, asbestos bodies and fibers, and infectious organisms, especially those involved in opportunistic expressions.

5. Downward expansion to 8 yrs of age (or perhaps as young as 5) is warranted in view of the present finding that severe CAR and other lung lesions occur in youths 14 years of age. Consideration should also be given to ages from 25 to 50 for defining the evolution of the early lesions of the lung. Many questions concerning the relationship of CAR disease to the various forms of emphysema and fibrosis are still unanswered.

6. The quantitation of cell and tissue alterations that evolve into pathologic lesions has important potential as a means of gaining high sensitivity in morphometric measurements. Cell and tissue inventories are the ultimate needs for determining the rate of structural decline of the lung, and will provide baselines of great importance to physiologists and clinicians who wish to correlate their lung function data with structural alterations. Image analysis quantitation of cells and tissues can be accomplished with human lung tissues, but will require the expansion and refinement of present applications. The present study indicates that a true color detector is necessary for human lung applications because of dirt deposits, pulmonary congestion, and other color interfering factors. Image analysis is a critical need for detecting early emphysematous change, especially with respect to CAR disease. In the latter respect, the diazo replication method (using 60uM whole lung frozen sections) affords the contrast and sensitivity essential for the image analysis application.

7. The variations in the environment and in the individual host defense system are mainly responsible for the broad variation in the severity and extent of lung abnormalities that have been found in the present investigation. The study of the viability and vigor of lymphocyte subpopulations is an especially important area for investigation in that an increased susceptibility to disease is in large part a reflection of lymphocyte performance.

## BODY OF REPORT

### A. SCOPE, PURPOSE AND BACKGROUND

Animal studies that we and others have done have shown that ambient levels of air pollution cause cell and tissue damage that is not entirely reversible [1,2]. More direct evidence that air pollution has an adverse effect on the human lung has come from lung function studies of the well population, with and without exercise [3,4], and also through epidemiologic studies of morbidity [5]. More recently, microscopic examination of the lungs from coroner autopsy cases of young individuals was reported to "support the hypothesis ... that the beginnings of COLD (chronic obstructive lung disease) may be found in the lungs of young adults" [6], and that smoking and air pollution were implicated in a "multifactorial basis of the tissue injury". The report concluded that the study "lends significant support to the validity of the postmortem epidemiologic approach". However, the question of validity has not been fully answered in that a number of factors involving feasibility have not been fully explored, in particular the availability of pathologic-demographic correlates that can address the question of air pollution effects apart from the other multifactorial aspects.

The immediate goal of this proposal was to demonstrate the feasibility of obtaining, processing, and analyzing lungs from ostensibly healthy young individuals (Medical Examiner-Coroner autopsy cases of violent deaths). Individuals ranging from 15 to 25 years of age were selected in order to minimize confounding pathologic lesions and changes in residence, and at the same time be able to find lung abnormalities at levels adequate for epidemiologic purposes. The major specific goals of feasibility were to demonstrate the following: the availability of a sufficient number of lungs of young individuals for study, the suitability of the lungs for the kinds of tests and measurements planned, the presence of lesions that can serve as discriminants for defining the role of air pollution in the development of lung disease, the sensitivity of methodologies available for the identification and quantitation of lung lesions, the interrelationships of the various kinds of lung lesions with each other, and the availability of demographic, historical and laboratory data (e.g. blood tests) for correlation with the pathologic findings and ultimately with the high and low levels of air pollution of the different communities involved.

Another important aspect of feasibility was the establishment of a close working relationship with the staff and relevant personnel of the MEC office. In effect, a team effort was required that involved a strong commitment of time and effort by MEC staff for the both the lung acces-

sioning and demographic part of the investigation. As part of a mutually beneficial arrangement, the feasibility of serving as a volunteer consultant to the MEC staff, in return for commitments to the project, became a part of the project demonstration.

A longer term aspect of feasibility was the derivation of air pollution data from data banks under the direction of the California Air Resources Board, and ultimately correlations with zip codes and/or other demographic markers of residence. It was recognized that the target number of 150 cases would answer the basic feasibility questions involved but would not afford a sufficient number of cases for a definitive correlation of lung injury with place of residence.

## B. Rationale and Objectives

Animal studies that we and others have done have shown that ambient levels of air pollution cause injuries to cells and tissues [7-12]. There is also a large body of data from clinical and epidemiologic studies of the human lung implicating air pollution at ambient levels as injurious to the lung and health in general. However, there is very limited information on structural damage to the human lung that is related to air pollution. Preliminary type data suggest a greater prevalence of emphysema in commmunities with high levels of air pollution [13,14] and, as noted above, a pilot postmortem-epidemiologic study [6] has provided support for the feasibility of correlating the presence of lesions in the lungs of young individuals with noxious agents in the environment. A finding of special pertinence is the relatively common presence of respiratory bronchiolitis in young individuals, i.e. 5 of 20 non-smokers (25%) and essentially all 19 smokers [15]. While the respiratory bronchiolitis was considered to be an incidental finding without clinically detectable effects, there is a growing body of evidence linking the bronchiolitis to abnormal lung function and to clinical disease [16,17]. The main significance of the bronchiolitis for our purposes is that its relatively common presence lends itself to use as a discriminant for identifying varying levels of lung injury. Moreover, since the basic lesion of the bronchiolitis, but devoid of the particulate-pigment component, has been observed following the exposure of animals to ambient levels of ozone and/or nitrogen dioxide [12,18], some modulation of the severity and extent in both smokers and non-smokers can be expected from exposure to community atmospheres with high levels of air pollution. The bronchiolitis is a special concern for Los Angeles County since the basic lesion has been produced by exposing primates to 0.15 ppm ozone for 90 days [19] and the County frequently experiences exceedences of the Federal Standard for ozone (0.12 ppm). On the basis of the most recent data, and from the cumulative data to date, there is now little doubt that air pollution has some adverse effect

on the human lung. However, the magnitude of its adverse impact on health is not clear since a convincing link between air pollution and the causation of serious lung disease has not been achieved. Accordingly, the present investigation is attempting to establish the extent and severity of structural damage in the human lung with ultimate goal of determining the role that air pollution is playing in the causation, promotion, facilitation, and/or exacerbation of the damage. In effect, we are searching for the structural counterpart to the decline of lung function that is ubiquitous in the well population. There are preliminary data suggesting an accelerated decline in lung function attributable to air pollution [4]. An accelerated rate of decline in lung structure would lead to a premature depletion of lung reserves and in the process progressively increase susceptibility to disease in general as well as cause clinical disease.

With respect to the specific objectives of the feasibility demonstration, we asked three main questions:

1) Can we obtain sufficient numbers of lung specimens from the Los Angeles County Medical Examiner's Office for pathological examination, morphometry, and ultimate epidemiologic/demographic correlations? More specifically, the criteria for selection were: cases in the 15-25 years of age group, Los Angeles County residents, sudden death (to avoid treatment complications), no history of disease or gross evidence of disease at autopsy, no history or evidence of drug use, and one lung (left or right) technically suitable for study (e.g. no laceration or contusion). The reason for selecting a group 15 to 25 years of age was the need to optimize the presence and identification of the early lesions of destructive lung disease. Also, the relatively young age would tend to mimimize change of residence, occupational type exposures, pack-years of smoking and/or drug use, and clinically manifested disease. On the other hand, precursor lung lesions would be present to some extent along with some degree of overt pathology such as emphysema, i.e. all adult lungs have more than trace amounts of emphysema [20].

2) Can the methodologies proposed provide the kinds of morphometric data and information on lesion identification that can be of practical use for epidemiologic correlations?

3) Can epidemiologic data be obtained that will appropriately meet the needs of the ultimate goal, namely a search for a correlation between the amount of lung damage and the level of air pollution according to monitoring station locations throughout Los Angeles County?

To answer the foregoing principal questions, we set up the following specific procedures:

1) accessioning of lungs from a randomly selected, ostensibly healthy group of youths (15 to 25 year old) from the well population.

2) processing of lungs and evaluation of adequacy, i.e. numbers, proper perfusion-inflation, and tissue preservation.

3) pathologic examination of the lungs for abnormalities at the gross and microscopic levels, and for adequacy of sampling with respect to the evaluation of the severity and extent of lesions observed.

4) identification of distinctive lesions warranting tabulation and quantitation, and the development of methodologies for obtaining morphometric data on pathologic changes, including amounts of emphysema, pigment deposits, status of submucosal glands, and presence of bronchiolitis.

5) quantitative image analysis for deriving data on cell and tissue abnormalities, including feasibility tests for the detection of cells and tissues at various postmortem intervals through special stains. namely lactate dehydrogenase for Type 2 cells and alveolar walls, aldehyde fuchsin for elastin, and Periodic Schiff for mucous glands of bronchi.

6) processing and quantitation of subpopulations of lung lymphocytes. Determine viability of the cells according to postmortem interval and preservation of membrane receptors for subpopulation identification;

7) protocols for an epidemiologic study, including forms for letters and telephone interviews of next of kin.

8) evaluations of sources and mechanisms for the retrieval of air quality data from the monitoring station network, and development of protocols for correlative needs, e.g. ZIP codes and census tracts;

9) protocols for collating data and performing statistical analysis;

## C. MATERIALS AND METHODS

### Preliminary Preparations

A first step was to establish the availability of lungs from the well population in cooperation with the Medical Examiner of the County of Los Angeles, a large metropolitan area having frequent exceedences of air quality standards. A check of Medical Examiner records showed that several hundred cases of vehicular accidents and homicides involving young individuals were potentially available each year for the study. An investigative team was organized to develop protocols for procedures involving the pathologic and epidemiologic aspects.

### Preparation of Facilities and Materials for Processing of Lungs

A room in the Research Building of the Los Angeles County-USC Medical Center nearby the MEC Office was set up for the handling, perfusion-fixation, and storage of the lungs. The equipment needed for processing the lungs (pump with special filter system, rotary slicer, plastic package sealer) was put into working order, and the necessary precautionary measures for handling hazardous materials (e.g. AIDS and hepatitis) were instituted. The USC Safety guidelines for handling tissues, cleaning, and disposal of contaminated materials were used. Disposable gowns, gloves. plastic bags, paper towels were discarded into specially provided infectious waste containers. All soiled materials, including table tops and instruments, were decontaminated with 10% Chlorox solution. Arrangements for on site hazardous waste cans and liners and the routine removal of soiled and hazardous materials were carried out by the USC Safety Office.

### Lung accessioning

The initial procedure was to check the postmortem listing each morning at the Medical Examiner's Office. Cases were selected by the Principal Investigator personally and according to the following criteria: sudden death of a Los Angeles County resident 15-25 years of age inclusive, no historical or evidence on examination of disease or drug abuse, and no gross lung abnormality such as trauma, laceration, or hemorrhage. The lungs were transported in a lid-sealed plastic container with plastic bag enclosure to a close-by laboratory equipped for the handling of hazardous materials (hepatitis and AIDS, in particular). Hilar lymph nodes were excised for the immunopathologic studies (Dr. A. Richters), the bronchus cannulated, and the label-identified lung suspended in a 100 liter container of 10% phosphate-buffered formalin, with the bronchial cannula connected to a continuous perfusion-inflation device for a minimum of 24 hours and usually over 48 hours.

**Tissue Processing**

Following fixation, the lung was washed in running tap water, measured and photographed. The gross descriptions of the lung included the following measurements: superobasal (vertical) height, anteroposterior depth, and mediolateral width. Descriptions of the pleural surfaces and general external appearance were dictated at the time of examination. Rotary slicer sectioning at approximately 10mm thicknesses afforded a representative display of the entire cut surface, and the display was photographed before and after the selection of tissue samples for paraffin embedment. The sections routinely taken were the central portion of the left lower lobe (posterolateral area), the basal portion of the left lower lobe (lateral area), the central portion of the left lower lobe (anteromedial area), the apical portion of the left lower lobe (superoanterior area), and the main stem bronchus approximately 5mm from the segmental division. The selected tissues were placed in cassettes for routine paraffin embedment processing. All remaining tissues were sealed in a plastic envelope containing formalin and stored.

Hematoxylin and eosin stained sections of each of the above tissues were processed by the histopathology section of the department. A semiquantitative scoring measurement (1-10 severity; 1-10 extent) was done for each case, with independent data recording for each of the five sections (4 lung sections and one bronchial section). Image analysis quantitation used an aldehyde fuchsin stain to identify lung elastin and a periodic acid-Schiff (PAS) stain to identify the secretory material of mucous glands.

A representative section of the entire left upper lobe was embeded in a gelatin solution [21] stored at $+4^{o}C$ or $-20^{o}C$, and subsequently sectioned. Initially the proposed Whimster methodology was used. However, the preliminary results indicated that we were probably not detecting early stages of emphysema, and therefore a diazo methodology developed earlier [22] was substituted. The methodology required gelatin embedment and used a Tetrander sledge microtome for "giant sections" of lung. The lungs were sectioned at 60uM thicknesses and examined through diazo replica prints (high contrast images of the lung section), and also through direct observations of the lung sections by stereomicroscopy. The lung sections were stored after printing and examination by sealing them in plastic envelopes. The paraffin blocks of the five lung sections were also stored after sectioning.

**Histopathologic examination and quantitation**

The slides from each case were initially screened for an overview of pathologic abnormalities. Four lung sections from the first 40 cases processed were evaluated for abnormalities of structures distal to the terminal bronchiole (within the acinus), and semiquantitative measurements were made. In this first screening, we examined all four sections, evaluated them on a scale of 1-10 for severity and 1-10 for extent, and on completion of the readings from all four slides, recorded an average based on the overall impression (Table 1). We then repeated the entire evaluation independently of prior results and with a total of 107 cases, but this time recording the severity and extent of lesions in each of the four slides. Severity per slide was scored according to the highest level reached, and extent according to relative frequency of CAR involvement per slide (Table 2).

In addition to the lung tissue measurements, three sections of mainstem bronchus were examined and quantitated by both a semiquantitive subjective method and objective image analysis. The former (one H&E section) was used to evaluate the severity and extent of chronic inflammation in the mucosa and submucosa, and the latter (two PAS stained sections) were used to measure the relative amount of mucous gland secretion per unit of gland and per unit of submucosa delimited by the gland. Image analysis was also applied to measurements of elastin content of acini.

**Quantitative Image Analysis**

1) **Detection**

A Cambridge 720 Image Analyzer with a shading corrector and recording terminal (cassette tape and print out) was used to obtain measurements of lung elastin, alveolar wall [7], and mucous glands. The levels of detection were set by matching the electronically detected image (electronically "captured" image of the video picture) to the displayed image (simple TV video picture), and by comparing the displayed image with the actual microscopic field. The two image detectors of the analyzer operates on the basis of gray level separation. One detector was set to pick up only very dark objects, i.e. elastic fibers or mucous positive areas at a level which resulted in no change between the area of elastic fibers or the mucous area as seen on the in the video display of the microscopic image, and that observed in the positive electron image displayed by the detector system. The numbers of elastin fibers or glands detected were "fine-

tuned" by comparing by manual counting how well the electronic detection matched the "flagging" signals in a selected area of the video display. The detected image was also compared to the field observed through the microscope.

To pick up the lighter objects, a second detector was used for measurement of alveolar wall, and mucous and submucosal areas, its perimeters and linear intercepts. It was set at a level at which it picked up all shades of gray at or above the second setting. Comparisons between video display, electronic image and microscopic fields were made to effect the best representation of the alveolar wall area with minimal background "noise." With the two detector settings set for elastin or mucous and wall area, an automatic program was used for measurement recordings. The quantitative measurements were recorded on cassette tape using a data terminal, and the cassette data then "captured" on floppy disks through a computer program. The data were formatted in accordance with statistical package (BMDP) requirements. A 10X ocular and 16x objective were used for the quantitation of elastin fibers, and 6.3x for mucous gland quantitation. All measurements were carried out by Dr. V. Richters to ensure consistency in the image analysis quantitation.

2. **Quantitative Measurements of Submucosal Mucous Glands**

The following tissues were selected and criteria set up for image analysis quantitation of mucus glands and mucous cells:

a. The main stem bronchus was selected for quantitation since it provided the most uniform presentation of submucosal glands. The defined measurements included: a) total submucosal gland area, b) combined submucosal gland area and submucosal connective tissue area, and c) PAS positive mucus content of submucosal glands;

b. Cartilage with its underlying submucosa must have a length equivalent to that of the measuring field of the video monitor.

c. The bronchial cartilage underlying the submucosal glands must be continuous.

c. Areas of submucosa having smooth muscle were not used.

d. Mucosa, if present, was excluded from measurements.

Lymphocyte Study: Preparation, Staining and Quantitation

The relative numbers of T Lymphocyte subpopulations [23] were obtained by random sampling of hilar lymph node tissue at a level between the carina and the right or left hilum. It was placed in a sterile Petri dish on a moist sponge and transported to the laboratory for processing for lymphocyte subpopulation studies.

Single cell susupensions were prepared by finely cutting the nodal tissue and then gently pressing the minced tissue through a fine stainless steel mesh using a rubber policeman. The cells were then suspended in $Ca^{2+}$ and $Mg^{2+}$-free Earle's balanced salt solution (EBSS). The cell suspensions were washed twice in EBSS by centrifuging at 400Xg for 10 minutes at $4^{o}C$.

The quantitation was carried out using the following monoclonal antibodies:

a. anti-Leu2a to identify cytotoxic/suppressor T cells
b. anti-Leu 3a & 3b to identify T helper cells, and
c. anti-Leu 4 to identify all T lymphocytes

In addition, B lymphocytes and natural killer cells (NK) were quantitated using anti-Leu12 and anti-Leu 11a monoclonal antibodies, respectively. In a few isolated instances, spleen cell suspensions were also prepared, and the lymphocyte populations were labeled with three monoclonal antibodies, Lyt 1, Lyt 2, and Thy-1.2. The cell suspensions were centrifuged in basal salt solution (BSS), and after the second wash, the concentration of the cell suspensions were adjusted to $1x10^{6}$, and resuspended in 0.1ml of Dulbecco's modified Eagle medium supplemented with 5% horse serum (DMEM) in 12mm x 75mm plastic test tubes. Five ul of the appropriate fluorescein-conjugated monoclonal antibody (Dickinson Immunocytometry Systems) was added to the cell suspensions and incubated for 20 minutes on ice. The cells were then washed twice in EBSS and resuspended in 1ml of DMEM. A Cytofluorograf 50H (Ortho Pharmaceuticals) FACS was used to perform flow cytometric analysis. The fluorescein- and phycoerythrin-labelled cells were analyzed for forward light scattering, right angle light scattering, and fluorescence. The percentage of cells exhibiting fluorescence intensity above the background level were determined by fluorescence histograms generated by FACS-interfaced computer integration and by comparison of the sample to unstained control fluorescence histograms.

### Epidemiologic Study

The major part of the epidemiologic effort was committed to the development and approval by all participants of protocols for next-of-kin interviews, the participants including Medical Examiner's Office, UCLA, USC, and investigators. In addition, formats were prepared for letters of introduction and telephone interview questionnaires. The feasibility of the overall demographic program, including plans for interviewing the next-or-kin, was primarily assigned to a graduate student under the direction of Dr. Roger Detels and in cooperation with all investigators. Three approaches to interviews of the next-of-kin were effected, telephone, introductory letter followed by a telephone call, and interviews at the home of the next-of-kin. The interview questions were initially relatively extensive, but were reduced substantially in content in order to optimize the data yield.

## D. RESULTS

### Liaison with the Coroner's Office

With the investigation dependent on the availability of fresh lung specimens from the human well population, the first step of the project was to develop a liaison with the Chief Medical Examiner-Coroner Dr. Ronald L. Kornblum and the staff of the Los Angeles Medical Examiner-Coroner's Office (LAMCO).

The main effort of the organizational phase was directed to the establishment of liaisons between UCLA, USC, and Medical Examiner personnel, and with the participation of Dr. Raymond Neutra of the California Department of Health Services. The single most important need was to assure a close working relationship between the principal investigator and the professional staff of the Los Angeles Medical Examiner's Office. The latter included the Chief Medical Examiner (Dr. Ronald Kornblum), Mr. Steven Dowell (research director), the deputy medical examiners, and the resident pathologists. The Operating Officers and the pathologists performing the autopsies were contacted to explain the nature of the study, and the type of cases needed for the study. In addition, the cooperation of many others was essential, namely morgue attendants, record personnel, staff and outside investigators, histopathology technicians, and the secretarial-receptionist personnel. Formal meetings, presentations, and personal contacts were a key part of the start-up plans. To compensate the Deputy Medical Examiners in part for their added workload in assisting us, the principal investigator (Dr. Sherwin) afforded consultation services in three areas, on-site assistance with the interpretatio of gross anatomical findings, case diagnosis, and reports for publication. Further assistance was provided by co-

investigator (Dr. Valda Richters) who assumed the responsibility for service related needs, in particular the preparation of written reports on the lung specimens processed, photographic documentation of the gross appearance of all lungs before and after sectioning, and long term storage of all tissues for reference needs (Table 3).

During the early part of the study, the protocal for obtaining lungs for histological study and information for epidemiological evaluation was revised. Due to a heavy workload at the Coroner's Office, the accident cases were often "signed-out" by the MEC without an autopsy and this greatly reduced their availability. Homicide cases then became the main source of material for the study.

**Meetings**

Throughout the investigation, the participants held a number of meetings and telephone conferences to prepare needed documents, resolve problems, and discuss the progress of the project in general. The details of the meetings, including letters and revisions involved, have been summarized in Appendices A-F.

**Pathological Evaluation of Lung Tissue**

As a part of the pathologic investigation, reports on the gross examination before and after sectioning were prepared and submitted to the MEC Office. The gross observations have been supported by extensive photographic documentation, i.e. color prints of the intact lung, whole lung sections, and tissues removed for histopathologic examination (Table 3).

Certain lesions were given special attention with respect to definition and criteria for quantitation, namely chronic respiratory bronchiolitis, focal interstitial pneumonia, and focal fibrosis. Since respiratory bronchiolitis was found to vary from simple chronic inflammation of bronchiolar walls and histiocytic desquamation to complex lesions involving acinic structures other than respiratory bronchioles, the term "centriacinar region" (CAR) disease was applied. More specifically, the basic lesion of CAR disease is defined as chronic inflammation of respiratory bronchioles in association with histiocytic desquamation, with or without pigment phagocytosis by histiocytes. The basic lesion was initially designated "Peribronchiolar Desquamative Pneumonitis" (PDP) since histiocytic desquamation centered around the terminal bronchiole, involving respiratory bronchioles and their adjacent acinic structures. The more advanced lesions had four major additional or unusually prominent components: an infiltration of alveolar walls

by chronic inflammatory cells (multifocal, chronic interstitial pneumonia), intraalveolar histiocytic desquamation (focal, desquamative interstitial pneumonitis), peribronchiolar fibrosis, and centriacinar emphysema.

The pathologic study has provided preliminary results for the identification and quantitation of CAR disease. A total of 155 lungs were obtained from the Coroner's office. Lungs from 118 cases were processed and examined and 107 were suitable for analysis of centriacinar region (CAR) disease. The lungs from the 11 rejected cases had excessive congestion and/or hemorrhage, or the tissues were inadequately preserved (Table 4). The main finding was the presence of some degree of CAR disease in the majority, i.e. CAR disease was severe in the lungs of 29 cases, slight to moderate for 51 cases, and not observed for 27 cases. (Tables 5-7; Charts 1,2). There were lesions other than CAR disease. Chronic bronchitis was present in the lungs of all cases where tissues were available for examination (112/117; Chart 3). In the majority of instances (68; 62%) the inflammation within the submucosa was slight to moderate, using a scoring of 2-4 inclusive on a scale of 0-10. There were 6 cases (6%) with severe inflammation and 35 cases (32%) where the inflammation was minimal or absent. In three cases, the bronchial submucosa was considered to be inadequate for evaluation. The corresponding percentages for chronic inflammation involving the epithelial mucosal lining, as opposed to the underlying submucosal glands and periglandular tissue, were 12% severe, 64% slight to moderate, and 24% minimal or absent. There were 14 cases where the mucosa was too poorly preserved for evaluation, or missing entirely. There was also CAR disease without pigment phagocytosis by macrophages or associated pigment deposits (Chart 4), consistent with a viral or other noxious effect that was not complicated by particulate inhalation (general environment as well as smoking), hemorrhage, or other pigment phenomena. In the latter respect, a non-particulate primarily viral pathogenesis was suggested not only by the absence of had the additional support in a number of cases of an associated multifocal and chronic interstitial pneumonia, with and without exudative pneumonia (alveolar wall necrosis and intraalveolar proteinaceous exudates).

As mentioned earlier, the basic lesion of CAR disease was designated "peribronchiolar desquamative pneumonitis" (DPP) and represented the minimal lesion of macrophage desquamation within the lumina of respiratory bronchioles, with or without peripheral extension into acinic structures (alveolar ducts and alveolar sacs) and terminal (membranous) bronchioles. Peribronchiolar fibrosis included thickening of the wall by moderate to severe edema, macrophage infiltration, and/or fibrocollagenous proliferation.

## Image Analysis Study

### Quantitative Evaluation of Mucous Glands and Elastic Fibers

A total of 100 sections from 50 bronchi were stained with PAS and used for quantitative analysis of mucous glands. Sections from 35 lungs were stained with aldehyde fuchsin for the quantitation of elastic fibers.

Image analysis of lung elastin was hindered by the proteinaceous fluids and congestion of capillaries that often were found in the lung preparations. The problem was the limitations of the monochrome detector used, i.e. a true color detector for the image analyzer is needed for selection and accurate measurements.

The mucous glands and submucosal tissues were distinctly stained with the PAS methodology, and quantitative measurements were readily obtained of the PAS positive mucous cells, the gland itself (circumference and area), and the submucosal area that encompasses each gland. Technical difficulty was encountered with the image analyzer during the study, and this required a number of repeated measurements in order to maintain the baseline for the complete study. Repair of the instrument was not successful in that the full study could not be completed without a breakdown, and comparisons were not valid without maintenance of the baseline for all measurements. The image analyzer is outdated, and service is no longer provided by the company for its maintenance. The usefulness of the study was the demonstration of feasibility for the methodology.

The quantitative analysis of Type 2 cells was tentatively by-passed because of the special demands of handling hazardous tissues, in particular concern about sectioning unfixed tissue that may be infected with AIDS and hepatitis viruses.

## Lymphocyte Population Study

The fluorescent antibody cell sorter quantitation of lymphocyte subpopulations was partially successful in that labeling and measurement of T lymphocytes from hilar lymph nodes were achieved in 59 of 67 cases (88%), the others specimens being devoid of intact lymphocytes. Of the 59 cases, 39% had specimens yielding usable data on subpopulations, including a finding that 8% of the 59 were Leu 11 positive, i.e. were Natural Killer cells. The quantitation of B lymphocytes was unsuccessful.

Towards the end of the study period, a new service became available that could materially add to the feasibility of postmortem lymphocyte studies, namely an independently supported tissue transplantation project (cornea and other donor services) within the Medical Examiner's Office.

**Epidemiological Study**

The demonstration of feasibility for the epidemiologic phase of the study was partially successful in that the many obstacles encountered in effecting successful interviews with the next-of-kin appeared to be overcome by the end of the study. Certain positive aspects of feasibility warrant emphasis. It was first of all possible to achieve a cooperative working arrangement for the two universities (UCLA and USC) and the Medical Examiner's Office. Agreement on the content of letters to the next-of-kin and the format of the interviews was an important accomplishment. Very limited data were obtained from interviews, and this yield was due to the commitment during the latter part of the study of a highly motivated and capable graduate student. The single greatest obstacle for the interview process was the difficulty in contacting next-of-kin. A part of the difficulty was the use of a sequential order of contacting where the very first cases were used rather than the most current. The yield of interviews would undoubtedly be increased by the following changes in protocol: use of current case material, initial contact through a letter of introduction, and the exploitation of newly identified sources of information for locating the next-of-kin (property and mortuary divisions of the Medical Examiner's Office). Death certificate data was a main part of the retrieval effort for demographic information, providing the basic data of age, sex, residential address, birth place, occupation, and cause of death. The LAC-MEC investigator's report was used for additional details at the scene of death and also for commentaries of individuals (including relatives) at the scene.

The data obtained from the first 29 cases of the study where interviews were attempted were relatively limited (Appendix G). Of the 59, 17 could not be contacted because of no telephone listing in the reports provided by the Medical Examiner's Office, and of those contacted, 60% were successfully interviewed with respect to the approved protocol for telephone interviews (Tables 9-11). The net yield was very low, less than a quarter of the cases. We conclude that the feasibility demonstration was indeterminate, but that implementation of the recommendations made by the epidemiologists would ensure a sufficiently high yield of data. More specifically, the results to date indicate that the demonstration of feasibility is largely contingent on the availability of an experienced interviewer, one who would be fully committed to utilizing all the facilities and data sources identified in this preliminary study.

## Preliminary Demographic-Pathologic Correlations

Using the unconfirmed ethnic data, the ratio of minority groups to caucasians was almost 2/1 (62/38). However, the corrected data is expected to increase the ratio and also reverse the present caucasian dominance for the severe category of CAR disease. Of the 29 severe CAR disease cases, 14 were from Los Angeles, 7 from other cities in Los Angeles County, and 8 were of uncertain residence. For the slight to moderate and the no observed CAR disease cases, the ratios of LA city to LA county were reversed, 1/3 (11/30) and 1/1.3 (11/14), respectively (5-8).

Only very limited demographic-pathologic correlations can be made at this time. We have obtained very basic information (name, sex, age, residence, ethnic group) under the deliberate constraint of avoiding a bias to the pathologic study. Accessioning data was restricted to case number identification only, and data for this final report come from information supplied to us by Mr. Steve Dowell of the Medical Examiner's Office. Some presumed disparities have been noted in the preliminary data, in particular there were 51 cases with Hispanic surnames, but the immediately available records listed 18 as caucasian. Using the unconfirmed ethnic data, the ratio of minority groups to caucasians was almost 2/1 (62/38). However, the corrected data is expected to increase the ratio and also reverse the present caucasian dominance for the severe category of CAR disease.

Death certificate data was a main part of the retrieval effort for demographic information, providing the basic data of age, sex, residential address, birth place, occupation, and cause of death. The LAC-MEC investigator's report was used for additional details at the scene of death and also for commentaries of individuals (including relatives) at the scene.

## E. DISCUSSION:

The main objective of the study was to demonstrate the feasibility of using Medical Examiner cases to search for evidence that air pollution may be damaging the human lung. Feasibility was contingent on the achievement of three principal goals: accessioning a sufficient number of suitable lungs, finding lesions that have value as pathologic discriminants, and obtaining sufficient demographic and laboratory data. We believe that feasibility has been demonstrated in all three areas, with the acknowledgement that the demographic part of the study demonstrated that the needed mechanisms for data retrieval were available but fell short with respect to actual data retrieval.

The single most important demonstration of feasibility pertains to the finding of lung lesions with discriminant value. We demonstrated the presence of a wide spectrum in the nature and severity of lesions in the lungs of young individuals, with one fourth, and as young as 14, exhibiting severe and extensive CAR disease. Since some degree of CAR disease was present in the majority of the individuals, the CAR lesion affords a discriminant that is highly relevant to air quality evaluation. Pertinently, the CAR lesion is a common denominator for a number of noxious agents (see below), and the exposure of animals to levels of ozone as low as 0.15 ppm produces the basic components of the CAR lesion, i.e. a respiratory bronchiolitis with histiocytic desquamation and aggregation. The CAR animal lesion compares very closely to the lesions we found in youths with slight to moderate degrees of what is in effect a relatively mild form of subclinical lung disease. The one difference is the absence of pigment and particulate deposits in the animal model, but not all of the human lung lesions had the deposits. Our working hypothesis is that the human lung is repeatedly being assaulted from in utero life on by viruses and other infectious organisms, and that the resulting basic CAR lesion, without pigment and particulate deposits, later evolves into a number of lung diseases through interactions with diverse noxious agents. The diseases, e.g. emphysema, peribronchiolar fibrosis, and interstitial pneumonitis, are often not clinically manifested, but they nevertheless encroach on lung reserves and increase susceptibility to disease in general. It should be emphasized that all adult lungs have at least slight degrees of emphysema, and we suspect that a loss of half of the structural and functional reserves of the lung is not uncommon beyond the age of 50. From all of the foregoing considerations, and regardless of whether or not the youths with severe CAR lesions are representative of the well population, it is clear that a structural deterioration of the lung underlies the decline in lung function that is ubiquitous in the well population. The results of the present study raise the question of an acceleration in the rate of lung decline from the interaction of multiple agents, which includes air pollution since Los Angeles frequently exceeds the Federal Standard for ozone in particular. More specicifally, the pivotal question raised by the

high prevalence of CAR lesions in young individuals is how significant is the role of air pollution in the causation, promotion, facilitation, and/or exacerbation of the CAR lesion? Further, CAR lesions were not the only ones found; chronic bronchitis in particular was also commonly present, and to some extent apparently independent of the CAR lesion.

Other important aspects of feasibility were demonstrated. Lung accessioning and processing were very successful, demonstrating not only appropriate preservation of tissues but excellent cooperation on the part of the pathologists and staff of the MEC Office. The pathologic objectives were accomplished using only a relatively small part of the total case material potentially available, and there are innumerble opportunities for expansion of the investigation. The recent initiation of an organ and tissue transplantation project affords an excellent opportunity for optimizing the investigation of the host defense system, e.g. increased yield of viable lymphocytes. Also, providing assistance for the autopsy work can make a large number of vehicular accident and suicide deaths readily available (see Recommendations).

The demographic part of the project is considered to be feasible despite the limited data obtained, i.e. only 11/29 contacts for the 107 cases and only a 60% success rate for those that were contacted. The two resolvable problems were a late start in contacting next-of-kin (pending design and approval of letter of introduction and interview protocol) and a late identification of sources for contact. Once the contact protocols had been approved, it would have been more appropriate to start the interviews with the most recent cases accessioned rather than using cases from the beginning of the study. The "blinding" of the pathologist to demographic data was probably too strict since the close contact of the pathologist with the Medical Examiner staff would very likely have led to a much earlier identification of sources available for contacting next-of-kin. The single greatest need for the demographic study is information on smoking habits. Since a number of studies have shown that historical data is not reliable [24], the solution to this problem is testing for cotinine and cannabinoid levels. A survey of vehicular accident deaths and drug use (including marijuana) was carried out by the Medical Examiner's Office between 1983 and 1986, and was presumably to be extended to both homicides and vehicular accident deaths, but apparently was not followed through (see Table 12,13). Blood samples are routinely preserved for one year, but a loose coordination resulted in the salvaging of just 30 blood samples. However, routine accessioning specifically for the needs of the research project was put into effect for the latter part of study. In keeping with the "blinding" provision of the protocol and with lack of funds for supporting epidemiologic personnel, only minimal demographic data, and only from immediately available records, has been retrieved to date. Consequently, only limited interpretations are possible (see below).

A preliminary report of the pathologic findings has been recently accepted for publication [25]. A brief summary of the principal findings and their clinicopathologic significance is the following:

A severe and extensive CAR disease was found in the lungs of 29 of the 107 (27%) youths, and the majority (75%) had from slight to moderate disease. While smoking has been related (not exclusively) to the milder forms of CAR disease [15,26], the severe disease cannot be attributed to smoking alone. A number of other noxious agents are known to be involved in the pathogenesis, ozone exposure [19], asbestos [27], silica and silicates [28,29], and a variety of dusts and fumes from metals and particulates [30]. The peribronchiolar and focal interstitial fibrosis we observed in severe CAR disease has also been observed in diverse pneumoconioses. We could not establish silica, silicate, or asbestos as the prime factor involved in the pathogenesis. The controversial status of the smoking-asbestos relationship to peribronchiolar fibrosis has been discussed recently [27] and there is also a 1988 abstract report indicating an increasing incidence in smokers with aging and suggesting that smoking may be a contributory factor to lung fibrosis [31]. As we mentioned earlier, a working hypothesis is that frequent infections of the lung, especially prevalent in childhood, are adversely modulated by noxious environmental agents. We suspect that a number of noxious agents have interacted to cause the CAR disease observed in the subpopulation we studied. We excluded cases of overt disease and drug abuse, but A panel of hard drug tests is routinely carried out for homicides and vehicular accidents, but we have not retrieved the toxicologic data for the present study. Of pertinence, the results of an earlier survey on vehicular accident victims show a relatively high frequency of alcohol and drug use (Tables 12,13). In accord with the multifactorial causes of the CAR lesion in one or another of its forms, and with or without associated lesions (Tables 14-16), we believe that socioeconomic factors also play a role in the pathogenesis. Of special concern is a probable suboptimal conformation with childhood vaccination programs and the relatively unfavorable environment in general in which the majority resided. Central Los Angeles frequently exceeds Federal air quality standards, and there tends to be higher levels of air borne fumes, dusts. and molds in centrally located, congested, and poorer economic areas of the County. Also, demolition, as a part of redevelopment, tends to be comparatively greater.

The concern is that the high prevalence and severity of CAR disease represents a substantial depletion of the lung reserves of this subpopulation of young adults. While the subpopulation may be biased by the selection process, it may nevertheless be a bellwether of an accelerated rate of decline of lung structure for the well population in general. For the living cohorts of the subpopulation, there is the implication of premature exhaustion of lung reserves and a high incidence of clinically manifested lung disease over the long term. Synergistic effects between

lung infections, smoking, and air pollution are the immediate major concerns. We know of facilitated interactions between smoking and ozone [32] and also smoking with asbestos [33]. Particulates in the lung, a characteristic component of most CAR disease, not only have direct toxicant effects but adsorb, transport, concentrate, and retain noxious agents. For example, cigarette smoke greatly inhibits clearance of asbestos from the lung and increases the penetration of asbestos fibers [33,34]. We believe a similar mechanism is responsible for silicate pneumoconiosis, where pesticides, soil additives, and other noxious agents are transported to the acinus by particulates and become harmful putatively through toxic effects on the phagocytosing macrophages [29].

The clinical significance of CAR disease is only beginning to be appreciated. Progression to overt disease has long been suspected, and Myers and his co-workers have recently demonstrated clinical manifestations of CAR disease in the form of chronic interstitial lung disease [16]. They have also speculated that CAR disease may be a precursor of Desquamative Interstitial Pneumonitis [16]. In addition, Yousem and his co-workers [17] very recently reviewed 18 cases of interstitial lung disease and identified CAR disease (respiratory bronchiolitis) as the underlying cause. As we observed in our study, they [17] also found the severity of the disease to be greater than the "mild incidental histologic finding, respiratory bronchiolitis ... noted by Niewoehner and colleagues in autopsies of young cigarette smokers who died suddenly of non-pulmonary disease" [15]. All of the foregoing essentially confirm the principle advanced by Dunnill [35] that CAR disease, in particular the advanced form of centriacinar emphysema, has a greater impact on airflow than is ordinarily appreciated, namely that a lung with only 15% of its parenchyma damaged, but with the damage restricted to the CAR, would have 100% of its airflow altered to some degree. It should be emphasized that there is no sharp dividing line between CAR disease and emphysema. Further, while we are still struggling with the clinical and pathologic definitions of emphysema and other chronic obstructive pulmonary diseases (COPD), COPD as a whole has been rapidly rising [36-38], and with a wide variation [39], although the variation is probably largely due to differences in diagnostic practices. The rising incidence impacts on other organ systems in that forced vital capacity (FVC) was "second only to age" as a predictor of potential heart problems and mortality in women, and is rivaled only by blood pressure among men [40].

The morphometric methods established by Cosio and his colleagues in their correlations of lung function and small airway alterations [41] and used widely [33.42.43] have been explored in the developmental part of the pathologic workup. We believe that the labor intensive work needed to do such studies is not feasible for the large volume quantitation anticipated, and that the yield of information would be relatively limited. Our preliminary work in general indicates that

image analysis quantitation is highly feasible, and in fact demanded, for the high volume, high level of sensitivity, and high level of objectivity required for the ongoing studies. Measurements of centriacinar emphysema at relatively low levels is a critical need for quantitation of "early" dilatation, bearing in mind that a one millimeter dilatation of a 120 uM alveolar space (not detectable on gross examination) will be a 500 fold volume change. Pertinently, of all the morphometric measurements used in three recent definitive attempts at clinicopathologic correlations, emphysema "was the major determinant of severe airflow obstruction" [38]. Since very little destruction and architectural distortion can have a major impact on air flow if most CAR zones are involved, the diazo replication method we have successfully demonstrated in the present study should be of great value for ongoing studies.

We believe that an expanded study of the host defense system is warranted by the present findings that postmortem tissue is amenable to the identification of lymphocyte subpopulations. The immune response is one of the key factors that determines susceptibility to the adverse health effects of air pollution. It is our working hypothesis that the two main reasons why only 15% of smokers develop clinically manifested COPD [44] are lack of substantive co-factors and a relatively intact host defense system. "Childhood Respiratory Trouble" (CRT), a term introduced by Burrows [45] is a special concern since it involves both direct injury to the lung and alteration of local and systemic lung immune function. Glezen [46], commenting on Gold's report [47], stated: "Regression analysis suggested that infection in early childhood had a greater influence than cigarette smoking in determining the geographic distribution of chronic bronchitis", and an "accelerated decline in pulmonary function was related largely to two factors: cigarette smoking and history of acute respiratory problems dating from early life". Further, "Virtually all children are infected with respiratory syncytial (RS) virus and at least one of the influenza and parainfluenza viruses by two years of age" ... the "Risk factors for development of at least one classification of 'lower respiratory infection' (bronchiolitis) include parental smoking, older siblings, and family history of asthma ... This may be translated to man that the early insult of the virus infection in the lower respiratory tract is an essential element of the development of chronic and persistent impairment ... Ultimately, definitive answers may be provided by selective prevention of early insults to the lungs -- specifically involuntary smoking and virus infections [46]". We would add to the pathogenetic consideration the factors of air pollution and the growing problem of air toxicants. Reducing any one of the known causes of CAR disease, and of course as many as possible, will unquestionably have a salutory effect on the rate of lung decline.

We found chronic inflammation of the bronchial tree in most of the lungs we examined, and we suspect that there is some relationship between chronic bronchitis and CAR disease. However, our preliminary results from this investigation do not support a close relationship, i.e. we found a disparity between the severity and extent of chronic bronchitis and that of CAR disease. In contrast to our overview screening of bronchitis according to the Reid Index (ratio of gland thickness to mucosal depth), our preliminary findings with image analysis measurements suggest an important potential for whole gland evaluation, including mucous cell atrophy as well as hypertrophy. (see Recommendations).

Certain pathobiologic features associated with CAR disease may have special usefulness in evaluating the full extent of CAR disease, in particular cell population shifts and connective tissue alterations. Hyperplasia of Type 2 cells of the alveoli and Clara cells of the membranous bronchioles is well known to follow the exposure of animals to ambient levels of air pollution, and to reflect early injury to the lining of the lung parenchyma, especially the ultrathin Type 1 cell of the alveolus. We did not attempt to quantitate cellular alterations through the frozen section technique in view of biohazards (e.g. AIDS, hepatitis) not entirely controlled for under the proposal. We also were not able to quantitate elastic tissue by image analysis since the human lung has complicating tissue changes that require the use of a true color detector for the image analyzer.

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## ABBREVIATIONS

| | |
|---|---|
| AW | - Alveolar Wall |
| AWA | - Alveolar Wall Area |
| $C^0$ | - Centigrade |
| C | - Environmental Chamber |
| Ca | - Calcium |
| CAR | - Centriacinar region |
| EBSS | - Earle's Balanced Salt Solution |
| EDTA | - Ethylene diamine tetraacetic acid |
| gms | - grams |
| HMR | - Hoffman Research Building |
| hrs | - hours |
| LA | - Los Angeles |
| LDH | - Lactic acid dehydrogenase |
| LI | - Linear Intercept |
| Lyt-1 | - Helper inducer lymphocyte marker |
| Lyt-2 | - Cytotoxic/suppressor lymphocyte marker |
| Mg | - Magnesium |
| mg | - milligram |
| ml | - milliliter |
| NK | - Natural Killer lymphocytes |
| $NO_2$ | - Nitrogen Dioxide |
| $O_3$ | - Ozone |
| P | - Perimeter |
| pphm | - parts per hundred million |
| ppm | - parts per million |
| T2 Cell | - Type 2 Cell |
| Thy-1.2 | - Thymus derived lymphocyte marker |
| ul | - microliter |
| um | - micrometer (micron) |
| USC | - University of Southern California |

TABLE 1

PATHOLOGICAL FINDINGS

CASE ID _____

| | Severity | Extent |
|---|---|---|
| | 0-10+ | 0-10+ |
| Bronchitis, chronic<br>mucosal<br>glandular | | |
| Bronchiolitis, chronic | | |
| Desquamative peribronchiolar pneumonitis | | |
| Desquamative interstitial pneumonitis | | |
| Chronic interstitial pneumonia | | |
| Fibrosis, peribronchiolar | | |
| Emphysema | | |
| centrilobular | | |
| panlobular | | |

TABLE 2

PATHOLOGICAL FINDINGS

CASE ID _____

| Pathology | Severity 0-10+ | | | | | Extent 0-10+ | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Source | | | | | Source | | | | |
| | 1 | 2 | 3 | 4 | Ave | 1 | 2 | 3 | 4 | Ave |
| Bronchiolitis, chronic | | | | | | | | | | |
| Desquamative peribronchiolar pneumonitis (DPP) | | | | | | | | | | |
| Desquamative interstitial pneumonitis (DIP) | | | | | | | | | | |
| Chronic interstitial pneumonia (CIP) | | | | | | | | | | |
| Fibrosis, peribronchiolar | | | | | | | | | | |
| Emphysema centrilobular | | | | | | | | | | |
| panlobular | | | | | | | | | | |
| Anthracotic pigment | | | | | | | | | | |

| Bronchitis, chronic | Severity 0-10+ | Extent 0-10+ |
|---|---|---|
| mucosal | | |
| glandular | | |

TABLE 3

DATE OBTAINED:

AUTOPSY #:

PROCESSING: The fresh lung, received in a closed plastic container, was labeled and the bronchus cannulated with a short plastic tube. The lung was immersed in a large drum of 10% formalin and the bronchial tube attached to one of the outflow ports of the inflation device. Formalin inflation at 25 cm water pressure was effected over a minimum of two days through a reservoir connected to a recirculating pump. Following fixation, the lungs were washed and multiple sections obtained by means of an elctrical rotary slicer. Color photographs were taken (prints) before and after the removal of sections for histopathologic study.

LUNG EXAMINED: Left lung

| MEASUREMENTS: | | |
|---|---|---|
| | Superobasal height | - 17.0 cm |
| | Anteroposterior depth | - 13.0 cm |
| | Mediolateral width | - 6.0 cm |

GROSS DESCRIPTION:

On the postero-medial surface, lower lobe, there are several cystic dilatations which protude slightly from the surface, the largest of which measures 2.0 cm x 1.5 cm in surface cross diamter. On palpation, a finger can be depressed approximately 1.5 cm into the parenchyma borded by the cystic space. Slight to moderated milky streaking is noted on the medial and lateral surfaces of the lingula, and to a slight extent on the diaphragmatic surface of the lower lobe. On cutting through the bulla, a cavernous space is noted measuring approximately 2 cm in diameter. On incision, the space extends both inferiorly and superiorly for additioanl 1 cm each, but in a conical fashion with some surrounding lung tissue. The dome of the bulla has transparent pleural lining of approximately 0.4 cm in diameter. The bronchovascular structures are unremarkable.

Left lower lobe sliced: 9 slices.

On cut section, the cystic space measures in greatest diameters 4.0 cm x 1.5cm. The periphery of the cystic space does not have an obvious connection with bronchial tree, and is therefore considered a bullous cyst. Moreover, the upper half of the left lower lobe shows a patchy cystic type of thinning of the parenchyma with multiple confluent cystic spaces which appear to be more centrilobular than panlobular. However, the apical portion over a roughly 3 sq cm in greatest involvement appears to be slightly to moderately panloabular. Photographs have been taken before and after compression of the lung manually to emphasize the naked thinning and loss of parenchyma in the upper half and to some extent in the central basilar region, lateral aspect.

MICROSCOPIC SECTIONS:

#1 - posterolateral, central
#2 - lateral, basal
#3 - anteromedial, high
#4 - superoanterior
#5- LLL bronchus
#7 - Pleural surface
#8 - Lateral portion, apical
#9 - Cystic lining

TABLE 4 (1)

DISTRIBUTION OF INCIDENCE OF CENTRIACINAR REGION DISEASE ACCORDING TO SEVERITY

Pilot Study of Accident Cases in Los Angeles County
15-25 year adults

| Case ID | Residence | AGE | SEX RACE | CAR | DIP | CIP | Chronic Bronchiolitis | Fibrosis Peri-bronchiolar | Emphysema | | Anthracotic pigment | Bronchitis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | CLE | PLE | | mucosal | submucosal |
| 89- 2759 | Claremont | 18 | M/C | 9 | 5 | 4 | 6 | 1 | | | 1 | 2 | 2 |
| 89- 2901 | Los Angeles | 22 | M/CS | 9 | | | 1 | 4 | | | 6 | 1 | 3 |
| 88- 4774 | Lancaster | 23 | M/C | 9 | | | 4 | 4 | | | 5 | 1 | 1 |
| 87- 8734 | No city | | | 8 | 5 | 2 | 3 | 1 | | | ND | 1 | 2 |
| 88- 4740 | Carson | 22 | M/N | 8 | | 3 | 5 | 3 | | | 3 | 3 | 5 |
| 88- 9061 | Gardena | 20 | M/C | 8 | | | | | 1 | | 3 | 1 | 1 |
| 88-12630 | Los Angeles | 24 | M/C | 7 | 4 | 5 | 4 | 3 | | | 4 | 1 | 5 |
| 87- 8835 | No city | | | 7 | 2 | 3 | 4 | 3 | | | ND | 2 | 2 |
| 88- 4968 | Los Angeles | 23 | M/N | 7 | 2 | 2 | 1 | 4 | | | 5 | 1 | 2 |
| 89- 5046 | No city | 25 | M/C | 7 | 2 | | 1 | 7 | 1 | | ND | 2 | 2 |
| 89- 4083 | Los Angeles | 23 | M/C | 7 | 3 | 3 | 3 | 3 | | | 6 | 2 | 2 |
| 88- 7682 | Los Angeles | 18 | M/CS | 7 | 2 | | 2 | 2 | | | 4 | 1 | 3 |
| 88-11788 | Los Angeles | 25 | M/C | 7 | | | 2 | 2 | | | 4 | 5 | 3 |
| 88- 6238 | Chihuahua | 21 | M/CS | 7 | | | 3 | 2 | | | 6 | 3 | 1 |
| 88- 8985 | Los Angeles | 25 | M/C | 6 | 4 | | 3 | 7 | 2 | | 6 | | 5 |
| 88-11151 | John Doe | 25 | M/CS | 6 | 5 | | 1 | 4 | | | 6 | 2 | 4 |
| 87-10597 | Los Angeles | 18 | M/ | 6 | | 3 | 4 | 3 | | | 3 | 2 | 2 |
| 88- 7377 | Compton | 25 | F/N | 6 | | | 3 | 2 | | | 7 | 1 | 2 |
| 88- 6389 | Los Angeles | 23 | F/CS | 5 | 3 | 2 | 4 | 2 | 1 | | 4 | 5 | 4 |
| 89- 257 | Compton | 23 | M/N | 5 | 4 | 5 | 7 | 1 | | | 2 | 3 | 4 |
| 87-10603 | Los Angeles | 22 | M/ | 5 | 3 | 3 | 4 | | | | ND | 3 | 4 |
| 87-10671 | Los Angeles | 18 | M/ | 5 | 3 | 3 | 1 | | | | 3 | 2 | 4 |
| 88- 9040 | Compton | 22 | M/N | 5 | | 1 | 2 | 1 | | | 3 | 2 | 3 |
| 88- 8233 | No city | 16 | F/C | 5 | 3 | 2 | 2 | | | | 2 | 2 | |
| 87-11535 | Los Angeles | 14 | M/ | 5 | | | | 4 | 2 | | 4 | TD | 4 |

TABLE 4 (2)

| Cases | | AGE | SEX RACE | CAR | DIP | CIP | Chronic Bronchiolitis | Fibrosis Peri-bronchiolar | Emphysema | | Anthracotic pigment | Bronchitis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | CLE | PLE | | mucosal | submucosal |
| 89- 6599 | Los Angeles | 16 | M/N | 5 | 2 | 2 | | | | | 3 | 3 | 1 |
| 88- 13 | Los Angeles | 25 | F/C | 5 | | | 2 | | 1 | | 4 | 2 | 1 |
| 88- 3481 | No city | 22 | M/CS | 5 | | | 4 | | | | 2 | 3 | TD |
| 89- 7969 | No city | 19 | M/N | 5 | | | | | | | 2 | ND | ND |
| 88- 3436 | Los Angeles | 23 | M/N | 4 | 3 | 2 | 2 | 2 | 1 | | 3 | 3 | 2 |
| 88- 3072 | Los Angeles | 25 | M/CS | 4 | 4 | | 4 | 3 | | | 2 | 1 | 2 |
| 89- 7801 | Altadena | 26 | M/C | 4 | 2 | 2 | 4 | | | | 7 | 4 | 4 |
| 88- 9550 | Cudahy | 18 | M/CS | 4 | | | 1 | 2 | 1 | | 4 | 3 | 4 |
| 88- 6264 | Carson | 19 | F/N | 4 | 2 | | | 2 | | | 3 | 2 | 2 |
| 88- 7924 | Quartz Hill | 24 | M/CS | 4 | 1 | | 2 | | | | 4 | 2 | |
| 88- 374 | Rowland Heights | 21 | M/C | 4 | | | | | | | 3 | 2 | |
| 88- 4200 | Culver City | 16 | M/N | 4 | | | 3 | | | | 5 | 7 | 8 |
| 88- 4268 | Lakewood | 23 | M/C | 4 | | 1 | | | | | 4 | 3 | 5 |
| 88- 3827 | North Hollywood | 21 | M/C | 4 | | | 1 | | | | 4 | 2 | 2 |
| 88- 2272 | Lancaster | 22 | M/CS | 3 | | 3 | 4 | | 2 | | 5 | | |
| 89- 2991 | Los Angeles | 20 | M/N | 3 | 5 | 1 | | 5 | | | 2 | 1 | 1 |
| 89- 4186 | Lancaster | 16 | M/C | 3 | 2 | | 1 | | | | 3 | 1 | |
| 88- 7997 | Los Angeles | 16 | M/N | 3 | | | 2 | | | | 2 | 1 | 3 |
| 87-11419 | Los Angeles | 24 | M/N | 3 | | | 5 | | | | 3 | TD | 4 |
| 88- 3590 | El Cajon | 19 | F/C | 3 | | | 1 | | | | 2 | 2 | 3 |
| 89- 7941 | No city | 25 | M/N | 3 | | | 1 | | | | 4 | 3 | 3 |
| 89- 60 | Erroneous ID | | | 3 | 2 | | | | | | 3 | 1 | |
| 88- 8012 | Walnut | 20 | M/C | 3 | | | | | | | 2 | 5 | 5 |
| 89- 6478 | Pico Rivera | 21 | M/C | 3 | | | | | | | 3 | 4 | 2 |
| 89- 3323 | Los Angeles | 5 | F/N | 3 | | | | | | | 1 | 2 | |
| 89- 4012 | Gardena | 16 | M/N | 3 | | | | | | | 1 | 3 | 3 |
| 89- 52 | Los Angeles | 20 | M/CS | 3 | TD | TD | TD | TD | TD | TD | 5 | 2 | 5 |
| 88- 3758 | Torrance | 24 | M/N | 3 | | | | | | | 2 | 1 | 2 |
| 88- 3762 | Canoga Park | 14 | F/CS | 2 | | 1 | 5 | | | | 3 | 2 | 4 |
| 88-11896 | Puerto Rico Barrios | 22 | M/C | 2 | | | 5 | 3 | | | 2 | 1 | 2 |
| 89- 4914 | Los Angeles | 14 | M/CS | 2 | 2 | | 2 | | | | ND | 3 | 3 |

TABLE 4 (3)

| Cases | | AGE | SEX/ RACE | CAR | DIP | CIP | Chronic Bronchiolitis | Fibrosis Peri-bronchiolar | Emphysema | | Anthracotic pigment | Bronchitis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | CLE | PLE | | mucosal | submucosal |
| 87-12732 | No data | | | 2 | | | | 5 | | | 6 | 3 | 3 |
| 88- 4815 | Hawthorne | 25 | M/N | 2 | 3 | | | | | | 1 | 1 | 3 |
| 88- 5252 | Panorama City | 22 | M/C | 2 | | | 2 | | | | 1 | 1 | 1 |
| 88- 9290 | Los Angeles | 17 | M/N | 2 | | | 1 | | | | 3 | TD | 3 |
| 88-11303 | Pueblo Nuebo | 18 | M/C | 2 | | | | 3 | | | 5 | 2 | 5 |
| 88- 8226 | La Puente | 18 | M/CS | 2 | | | | | | | 2 | 2 | 3 |
| 88- 9115 | Erroneous data | | | 2 | | | | | | | 1 | 5 | 2 |
| 88-11996 | Rowland Heights | 16 | M/C | 2 | | | | | | | 1 | ND | ND |
| 88-11997 | Rowland Heights | 18 | M/C | 2 | | | | | | | 2 | 2 | 1 |
| 89- 2859 | Compton | 18 | M/N | 2 | TD | TD | TD | TD | TD | TD | 2 | 2 | 2 |
| 89- 4853 | Wilmington | 22 | M/CS | 1 | 6 | 4 | 5 | 2 | 2 | | 3 | 2 | 1 |
| 89- 4502 | Palo Alto | 16 | M/N | 1 | 1 | 4 | 2 | | | | | 3 | 5 |
| 88- 5476 | Gonzales | 24 | M/CS | 1 | | | 1 | 3 | | | 5 | 3 | |
| 88-12011 | Compton | 21 | F/N | 1 | 4 | | 5 | | | | 1 | 4 | 1 |
| 88 -2832 | Lawndale | 24 | F/CS | 1 | | 2 | 1 | | | | 4 | 4 | 1 |
| 87-10482 | Compton | 19 | M/N | 1 | | | 3 | | | | 4 | 2 | 3 |
| 89- 4915 | Los Angeles | 20 | M/CS | 1 | 1 | | | | | | ND | 2 | 3 |
| 88- 7355 | Burbank | 23 | M/C | 1 | | | | | | | 3 | 1 | 1 |
| 88- 7566 | Glendale | 24 | M/C | 1 | | | | | | | 3 | 3 | 4 |
| 88- 8606 | Newhall | 25 | M/CS | 1 | | | | | | | 4 | 3 | 1 |
| 88-10980 | Erroneous data | | | 1 | | | | | | | 1 | 4 | 7 |
| 88- 5323 | Lynwood | 20 | M/N | 1 | | | | | | | 1 | 2 | 4 |
| 88- 6048 | Los Angeles | 21 | M/N | 1 | | | | | | | 2 | 2 | 2 |
| 89- 2989 | Van Nuys | 17 | M/CS | 1 | | | | | | | 2 | 2 | 4 |
| 89- 2867 | Lennox | 18 | M/C | 0 | 1 | 5 | 3 | | | | 2 | 3 | 3 |
| 88- 5479 | No city | 20 | M/CS | 0 | | | 3 | 3 | | | 4 | 1 | |
| 88- 5849 | Lancaster | 27 | F/C | 0 | | 2 | 1 | | | | 1 | 1 | 2 |
| 89- 2135 | Los Angeles | 19 | M/N | 0 | | 3 | 1 | | | | | ND | ND |
| 89- 2533 | Torrance | 22 | M/C | 0 | | 2 | 2 | | | | 3 | ND | ND |
| 88- 1439 | Los Angeles | 18 | M/CS | 0 | | | 1 | | | | 2 | | 2 |
| 89- 3284 | Canoga Park | 22 | M/CS | 0 | | 1 | | | | | 3 | 1 | 2 |

TABLE 4 (4)

| Cases | | AGE | SEX/ RACE | CR | DIP | CIP | Chronic Bronchiolitis | Fibrosis Peri-bronchiolar | Emphysema | | Anthracotic pigment | Bronchitis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | CLE | PLE | | mucosal | submucosal |
| 87- 8814 | Los Angeles | 26 | M | 0 | | | 4 | | | | 4 | 2 | 2 |
| 88- 3502 | Los Angeles | 16 | M/MV | 0 | | | | | | | 3 | 2 | 3 |
| 88- 3781 | Los Angeles | 23 | M/C | 0 | | | | | | | 2 | 3 | 3 |
| 88- 4086 | Compton | 16 | F/CS | 0 | | | | | | | | 1 | 3 |
| 88- 4703 | Long Beach | 19 | M/C | 0 | | | | | | | | 4 | 5 |
| 88- 5076 | Westlake Village | 24 | F/C | 0 | | | | | | | 2 | 2 | 2 |
| 88- 6380 | Los Angeles | 15 | M/CS | 0 | | | | | | | 2 | 5 | 1 |
| 88- 6820 | Los Angeles | 24 | M/C | 0 | | | | | | | 3 | 3 | 1 |
| 88- 7642 | Baton Rouge | 18 | M/N | 0 | | | | | | | 2 | | 1 |
| 88- 9033 | Hawthorne | 24 | M/CS | 0 | | | | | | | 3 | 2 | 3 |
| 88- 8042 | Portsmith | 24 | M/C | 0 | | | | | | | 3 | 2 | 3 |
| 88-11111 | Pomona | 17 | M/MC | 0 | | | | | | | 2 | 2 | 6 |
| 89- 293 | Los Angeles | 16 | M/CS | 0 | | | | | | | 3 | 2 | 1 |
| 89- 868 | Cerritos | 19 | F/C | 0 | | | | | | | 3 | 3 | 2 |
| 89- 2256 | Los Angeles | 16 | M/CS | 0 | | | | | | | 1 | ND | ND |
| 89- 5231 | Newhall | 13 | M/CS | 0 | | | | | | | 2 | 4 | 2 |
| 89- 5432 | Los Angeles | 25 | M/N | 0 | | | | | | | 2 | 2 | 4 |
| 87-11541 | San Pedro | 16 | M/CS | 0 | | | | | | | | 3 | 4 |
| 87-11553 | Compton | 23 | M/N | 0 | | | | | | | 2 | 2 | 3 |
| 88-12433 | Los Angeles | 23 | M/N | 0 | | | | | | | | | |
| 87-10675 | | | | TD | TD | TD | TD | TD | TD | TD | TD | 2 | 4 |
| 89- 297 | Lynwood | 25 | M/N | TD | TD | TD | TD | TD | TD | TD | 2 | 1 | |
| 89- 1807 | De Mar Ensenada | 18 | M/CS | TD | TD | TD | TD | TD | TD | TD | 2 | 2 | 3 |

Table 5

INCIDENCE OF CENTRIACINAR REGION DISEASE IN LOS ANGELES COUNTY
Severity 5-9

Total: 29 cases

| Residence | Sex | Ethnic Background | | | | | No. Cases |
|---|---|---|---|---|---|---|---|
| | | C | B | H | A | U | |
| Los Angeles | M/F | 4/1 | 2/0 | 2/1 | - | 5/0 | 14 |
| Compton | M/F | 2/1 | - | 2/1 | - | - | 3 |
| Carson | M/F | 1/0 | - | 1/0 | - | - | 1 |
| Gardena | M/F | 1/0 | - | - | - | - | 1 |
| Claremont | M/F | 1/0 | - | - | - | - | 1 |
| Lancaster | M/F | 1/0 | - | - | - | - | 1 |
| Unknown | M/F | 1/1 | 1/0 | 1/0 | - | - | 4 |
| No Information | M/F | - | - | - | - | 2 | 3 |
| ?Los Angeles Residence | M/F | - | - | 1/0 | - | - | 1 |

C - Caucasian
B - Black
H - Hispanic
A - Asian
U - Unknown

Table 6

INCIDENCE OF CENTRIACINAR REGION DISEASE IN LOS ANGELES COUNTY
Severity 1-4

Total: 51 cases

| Residence | Sex | Ethnic Background | | | | | No. Cases |
|---|---|---|---|---|---|---|---|
| | | C | B | H | A | U | |
| Los Angeles | M/F | - | 6/1 | 4/0 | - | - | 11 |
| Other cities | M/F | 13/0 | 8/2 | 6/1 | - | - | 30 |
| Unknown | M/F | - | 1/0 | - | - | - | 1 |
| No Information | M/F | - | - | - | - | 4 | 4 |
| ?Los Angeles Residence | M/F | 1/1 | 1/0 | 2/0 | - | - | 5 |

C - Caucasian
B - Black
H - Hispanic
A - Asian
U - Unknown

Table 7

INCIDENCE OF NO CENTRIACINAR REGION DISEASE IN LOS ANGELES COUNTY

Total: 27 cases

| Residence | Sex | Ethnic Background | | | | | No. Cases |
|---|---|---|---|---|---|---|---|
| | | C | B | H | A | U | |
| Los Angeles | M/F | 2/0 | 3/0 | 5/0 | 1/0 | - | 11 |
| Other cities | M/F | 4/3 | 1/0 | 5/1 | - | - | 14 |
| Unknown | M/F | - | - | 1/0 | - | - | 1 |
| ?Los Angeles Residence | M/F | 1/0 | - | - | - | - | 1 |

C - Caucasian
B - Black
H - Hispanic
A - Asian
U - Unknown

Table 8 (1)

DISTRIBUTION OF CENTRIACINAR REGION DISEASE ACCORDING TO RESIDENCE

Pilot Study of Accident Cases in Los Angeles County
15-25 year adults

| Case ID | Residence | AGE | SEX RACE | CAR | DIP | CIP | Chronic Bronchiolitis | Fibrosis Peri-bronchiolar | Emphysema | | Anthracotic pigment | Bronchitis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | CLE | PLE | | mucosal | submucosal |
| 89- 2901 | Los Angeles | 22 | M/CS | 9 | | | 1 | 4 | | | 6 | 1 | 3 |
| 88-12630 | Los Angeles | 24 | M/C | 7 | 4 | 5 | 4 | 3 | | | 4 | 1 | 5 |
| 88- 4968 | Los Angeles | 23 | M/N | 7 | 2 | 2 | 1 | 4 | | | 5 | 1 | 2 |
| 89- 4083 | Los Angeles | 23 | M/C | 7 | 3 | 3 | 3 | 3 | | | 6 | 2 | 2 |
| 88- 7682 | Los Angeles | 18 | M/CS | 7 | 2 | | 2 | 2 | | | 4 | 1 | 3 |
| 88-11788 | Los Angeles | 25 | M/C | 7 | | | 2 | 2 | | | 4 | 5 | 3 |
| 88- 8985 | Los Angeles | 25 | M/C | 6 | 4 | | 3 | 7 | 2 | | 6 | | 5 |
| 87-10597 | Los Angeles | 18 | M/ | 6 | | 3 | 4 | 3 | | | 3 | 2 | 2 |
| 88- 6389 | Los Angeles | 23 | F/CS | 5 | 3 | 2 | 4 | 2 | 1 | | 4 | 5 | 4 |
| 87-10603 | Los Angeles | 22 | M/ | 5 | 3 | 3 | 4 | | | | ND | 3 | 4 |
| 87-10671 | Los Angeles | 18 | M/ | 5 | 3 | 3 | 1 | | | | 3 | 2 | 4 |
| 87-11535 | Los Angeles | 14 | M/ | 5 | | | | 4 | 2 | | 4 | TD | 4 |
| 89- 6599 | Los Angeles | 16 | M/N | 5 | 2 | 2 | | | | | 3 | 3 | 1 |
| 88- 13 | Los Angeles | 25 | F/C | 5 | | | 2 | | 1 | | 4 | 2 | 1 |
| 88- 3436 | Los Angeles | 23 | M/N | 4 | 3 | 2 | 2 | 2 | 1 | | 3 | 3 | 2 |
| 88- 3072 | Los Angeles | 25 | M/CS | 4 | 4 | | 4 | 3 | | | 2 | 1 | 2 |
| 89- 2991 | Los Angeles | 20 | M/N | 3 | 5 | 1 | | 5 | | | 2 | 1 | 1 |
| 88- 7997 | Los Angeles | 16 | M/N | 3 | | | 2 | | | | 2 | 1 | 3 |
| 87-11419 | Los Angeles | 24 | M/N | 3 | | | 5 | | | | 3 | TD | 4 |
| 89- 3323 | Los Angeles | 5 | F/N | 3 | | | | | | | 1 | 2 | |
| 89- 52 | Los Angeles | 20 | M/CS | 3 | TD | TD | TD | TD | TD | TD | 5 | 2 | 5 |
| 89- 4914 | Los Angeles | 14 | M/CS | 2 | 2 | | 2 | | | | ND | 3 | 3 |
| 88- 9290 | Los Angeles | 17 | M/N | 2 | | | 1 | | | | 3 | TD | 3 |
| 89- 4915 | Los Angeles | 20 | M/CS | 1 | 1 | | | | | | ND | 2 | 3 |
| 88- 6048 | Los Angeles | 21 | M/N | 1 | | | | | | | 2 | 2 | 2 |
| 89- 2135 | Los Angeles | 19 | M/N | 0 | | 3 | 1 | | | | | ND | ND |
| 88- 1439 | Los Angeles | 18 | M/CS | 0 | | | 1 | | | | 2 | | 2 |
| 87- 8814 | Los Angeles | 26 | M | 0 | | | 4 | | | | 4 | 2 | 2 |

TABLE 8 (2)

| Case ID | Residence | AGE | SEX RACE | CAR | DIP | CIP | Chronic Bronchiolitis | Fibrosis Peri-bronchiolar | Emphysema | | Anthracotic pigment | Bronchitis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | CLE | PLE | | mucosal | submucosal |
| 88- 3502 | Los Angeles | 16 | M/MV | 0 | | | | | | | 3 | 2 | 3 |
| 88- 3781 | Los Angeles | 23 | M/C | 0 | | | | | | | 2 | 3 | 3 |
| 88- 6380 | Los Angeles | 15 | M/CS | 0 | | | | | | | 2 | 5 | 1 |
| 88- 6820 | Los Angeles | 24 | M/C | 0 | | | | | | | 3 | 3 | 1 |
| 89- 293 | Los Angeles | 16 | M/CS | 0 | | | | | | | 3 | 2 | 1 |
| 89- 2256 | Los Angeles | 16 | M/CS | 0 | | | | | | | 1 | ND | ND |
| 89- 5432 | Los Angeles | 25 | M/N | 0 | | | | | | | 2 | 2 | 4 |
| 88-12433 | Los Angeles | 23 | M/N | 0 | | | | | | | | | |
| 88- 4774 | Lancaster | 23 | M/C | 9 | | | 4 | 4 | | | 5 | 1 | 1 |
| 88- 2272 | Lancaster | 22 | M/CS | 3 | | 3 | 4 | | 2 | | 5 | | |
| 89- 4186 | Lancaster | 16 | M/C | 3 | 2 | | 1 | | | | 3 | 1 | |
| 88- 5849 | Lancaster | 27 | F/C | 0 | | 2 | 1 | | | | 1 | 1 | 2 |
| 89- 2759 | Claremont | 18 | M/C | 9 | 5 | 4 | 6 | 1 | | | 1 | 2 | 2 |
| 88- 4740 | Carson | 22 | M/N | 8 | | 3 | 5 | 3 | | | 3 | 3 | 5 |
| 88- 6264 | Carson | 19 | F/N | 4 | 2 | | | 2 | | | 3 | 2 | 2 |
| 88- 9061 | Gardena | 20 | M/C | 8 | | | | | 1 | | 3 | 1 | 1 |
| 88- 7377 | Compton | 25 | F/N | 6 | | | 3 | 2 | | | 7 | 1 | 2 |
| 89- 257 | Compton | 23 | M/N | 5 | 4 | 5 | 7 | 1 | | | 2 | 3 | 4 |
| 88- 9040 | Compton | 22 | M/N | 5 | | 1 | 2 | 1 | | | 3 | 2 | 3 |
| 89- 2859 | Compton | 18 | M/N | 2 | TD | TD | TD | TD | TD | TD | 2 | 2 | 2 |
| 88-12011 | Compton | 21 | F/N | 1 | 4 | | 5 | | | | 1 | 4 | 1 |
| 87-10482 | Compton | 19 | M/N | 1 | | | 3 | | | | 4 | 2 | 3 |
| 88- 4086 | Compton | 16 | F/CS | 0 | | | | | | | | 1 | 3 |
| 87-11553 | Compton | 23 | M/N | 0 | | | | | | | 2 | 2 | 3 |
| 88- 374 | Rowland Heights | 21 | M/C | 4 | | | | | | | 3 | 2 | |
| 88-11996 | Rowland Heights | 16 | M/C | 2 | | | | | | | 1 | ND | ND |
| 88-11997 | Rowland Heights | 18 | M/C | 2 | | | | | | | 2 | 2 | 1 |

TABLE 8 (3)

| Case ID | Residence | AGE | SEX RACE | CAR | DIP | CIP | Chronic Bronchiolitis | Fibrosis Peri-bronchiolar | Emphysema | | Anthracotic pigment | Bronchitis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | CLE | PLE | | mucosal | submucosal |
| 89- 4853 | Wilmington | 22 | M/CS | 1 | 6 | 4 | 5 | 2 | 2 | | 3 | 2 | 1 |
| 88 -2832 | Lawndale | 24 | F/CS | 1 | | 2 | 1 | | | | 4 | 4 | 1 |
| 88- 7355 | Burbank | 23 | M/C | 1 | | | | | | | 3 | 1 | 1 |
| 88- 7566 | Glendale | 24 | M/C | 1 | | | | | | | 3 | 3 | 4 |
| 89- 2989 | Van Nuys | 17 | M/CS | 1 | | | | | | | 2 | 2 | 4 |
| 89- 2867 | Lennox | 18 | M/C | 0 | 1 | 5 | 3 | | | | 2 | 3 | 3 |
| 89- 2533 | Torrance | 22 | M/C | 0 | | 2 | 2 | | | | 3 | ND | ND |
| 89- 3284 | Canoga Park | 22 | M/CS | 0 | | 1 | | | | | 3 | 1 | 2 |
| 88- 4703 | Long Beach | 19 | M/C | 0 | | | | | | | | 4 | 5 |
| 88- 5076 | Westlake Village | 24 | F/C | 0 | | | | | | | 2 | 2 | 2 |
| 88-11111 | Pomona | 17 | M/MC | 0 | | | | | | | 2 | 2 | 6 |
| 89- 868 | Cerritos | 19 | F/C | 0 | | | | | | | 3 | 3 | 2 |
| 87-11541 | San Pedro | 16 | M/CS | 0 | | | | | | | | 3 | 4 |
| 89- 5046 | No city | 25 | M/C | 7 | 2 | | 1 | 7 | 1 | | ND | 2 | 2 |
| 88- 8233 | No city | 16 | F/C | 5 | 3 | 2 | 2 | | | | 2 | 2 | |
| 88- 3481 | No city | 22 | M/CS | 5 | | | 4 | | | | 2 | 3 | TD |
| 89- 7969 | No city | 19 | M/N | 5 | | | | | | | 2 | ND | ND |
| 89- 7941 | No city | 25 | M/N | 3 | | | 1 | | | | 4 | 3 | 3 |
| 88- 5479 | No city | 20 | M/CS | 0 | | | 3 | 3 | | | 4 | 1 | |

TABLE 8 (4)

| Case ID | Residence | AGE | SEX RACE | CAR | DIP | CIP | Chronic Bronchiolitis | Fibrosis Peri-bronchiolar | Emphysema | | Anthracotic pigment | Bronchitis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | CLE | PLE | | mucosal | submucosal |
| 87- 8734 | No data | | | 8 | 5 | 2 | 3 | 1 | | | ND | 1 | 2 |
| 87- 8835 | No data | | | 7 | 2 | 3 | 4 | 3 | | | ND | 2 | 2 |
| 88-11151 | John Doe | 25 | M/CS | 6 | 5 | | 1 | 4 | | | 6 | 2 | 4 |
| 87-12732 | No data | | | 2 | | | | 5 | | | 6 | 3 | 3 |
| 87-10675 | | | | TD | TD | TD | TD | TD | TD | TD | TD | 2 | 4 |
| 88- 7924 | Quartz Hill | 24 | M/CS | 4 | 1 | | 2 | | | | 4 | 2 | |
| 88- 3590 | El Cajon | 19 | F/C | 3 | | | 1 | | | | 2 | 2 | 3 |
| 89- 4502 | Palo Alto | 16 | M/N | 1 | 1 | 4 | 2 | | | | | 3 | 5 |
| 88- 5476 | Gonzales | 24 | M/CS | 1 | | | 1 | 3 | | | 5 | 3 | |
| 89- 60 | Erroneous data | | | 3 | 2 | | | | | | 3 | 1 | |
| 88- 9115 | Erroneous data | | | 2 | | | | | | | 1 | 5 | 2 |
| 88-10980 | Erroneous data | | | 1 | | | | | | | 1 | 4 | 7 |
| 88- 7642 | Baton Rouge | 18 | M/N | 0 | | | | | | | 2 | | 1 |
| 88- 8042 | Portsmith | 24 | M/C | 0 | | | | | | | 3 | 2 | 3 |
| 88- 6238 | Chihuahua | 21 | M/CS | 7 | | | 3 | 2 | | | 6 | 3 | 1 |
| 88-11303 | Pueblo Nuebo | 18 | M/C | 2 | | | | 3 | | | 5 | 2 | 5 |
| 89- 1807 | De Mar Ensenada | 18 | M/CS | TD | TD | TD | TD | TD | TD | TD | 2 | 2 | 3 |

TABLE 9

CASES INTERVIEWED
Total: 11/29 cases

| Status of Interview | No Cases | % Subtotal | % Overall |
|---|---|---|---|
| Completed | 6 | 6/11 (54%) | 6/29 (21%) |
| Refused | 5 | 5/17 (29%) | 5/29 (17%) |
| Disqualified due to preexisting illness and age | 1 | 1/17 ( 9%) | 1/29 ( 3%) |

TABLE 10

CASES NOT INTERVIEWED
Total: 17/29 cases

| Reason for not Conducting Interview | No Cases | % Subtotal | % Overall |
|---|---|---|---|
| A. Reports at the Coroner's Office showed: | | | |
| No listing of phone number | 5 | 5/17 (29%) | 5/29 (17%) |
| Listing of wrong phone number | 5 | 5/17 (29%) | 5/29 (17%) |
| No phone | 4 | 4/17 (24%) | 4/29 (14%) |
| B. Listed phone number disconnected, no forwarding number | 3 | 3/17 (18%) | 3/29 (10) |

TABLE 11

CASES NOT QUALIFIED FOR INTERVIEW
Total: 1/29 cases

| Reason for Disqualification | No Cases | % Subtotal | % Overall |
|---|---|---|---|
| Subject too young | 1 | 1/1 (100%) | 3/29 (3%) |

Table 12

Comparison of the December 1983 Traffic Accident Drugs of Abuse Studies
Los Angeles County*

| Drugs Detected | Los Angeles County | | Other Counties | |
|---|---|---|---|---|
| | # Times Detected | % of Drivers with Drug (N=222) | # Times Detected | % of Drivers with Drug (N=218 |
| Alcohol | 148 | 67 | 160 | 73 |
| Marijuana | 69 | 31 | 93 | 43 |
| Cocaine | 24 | 11 | 23 | 11 |
| Diazepam | 8 | 4 | 11 | 5 |
| Phencyclidine | 17 | 8 | 1 | 0 |
| Methamphetamine | 0 | 0 | 14 | 6 |
| Phenylpropanolamine | 4 | 2 | 6 | 3 |
| Other Drugs | 26 | 12 | 14 | 6 |
| | 297 | | 333 | |

*Report of Los Angeles County Medical Examiners Office

Table 13

Comparison of the December 1983 and June 1986
Traffic Accident Drugs of Abuse Studies (Frequently Encountered Drugs)
Los Angeles County*

| Drug Detected | 1983 Study (N=222) | | 1986 Study (N=102) | | Two Studies Combined (N=234) | |
|---|---|---|---|---|---|---|
| | # Cases Positive | Percent Positive | # Cases Positive | Percent Positive | # Cases Positive | Percent Positive |
| Alcohol | 148 | 67% | 53 | 52% | 201 | 62% |
| Cannabinoids | 69 | 31% | 20 | 20% | 89 | 27% |
| Cocaine | 24 | 11% | 10 | 10% | 34 | 10% |
| Phencyclidine | 17 | 8% | 5 | 5% | 22 | 7% |

*Report of Los Angeles County Medical Examiners Office

TABLE 14

## PATHOGENESIS OF CAR DISEASE

Infectious organisms, e.g. indigenous/exogenous viruses

Smoking, tobacco and/or marijuana

Air Pollution, e.g. ambient ozone and nitrogen dioxide

Dusts & Fumes, occupational, paraoccupational, & community

e.g. silica, silicate, asbestos

Immunologic and hypersensitivity diseases

TABLE 15

CAR DISEASE is a Respiratory Bronchiolitis characterized by an intrabronchiolar histiocytic desquamation and chronic inflammation, with or without:

a. Pigment phagocytosis and/or interstitial deposition.
b. Bronchioloalveolar histiocytic infiltration.
c. Chronic Interstitial Pneumonia, localized or widespread.
d. Desquamative Interstitial Pneumonia, localized or widespread.
e. Peribronchiolar fibrosis.
f. Emphysema, centriacinar, panacinar, or other.
g. Exudative alveolitis (organizing pneumonia).
h. Epithelial hyperplasia.
i. Hyperplastic epithelial nodules.
j. Pulmonary Interstitial Fibrosis, localized or widespread.

CHART 1

# CENTRIACINAR REGION DISEASE

n=107

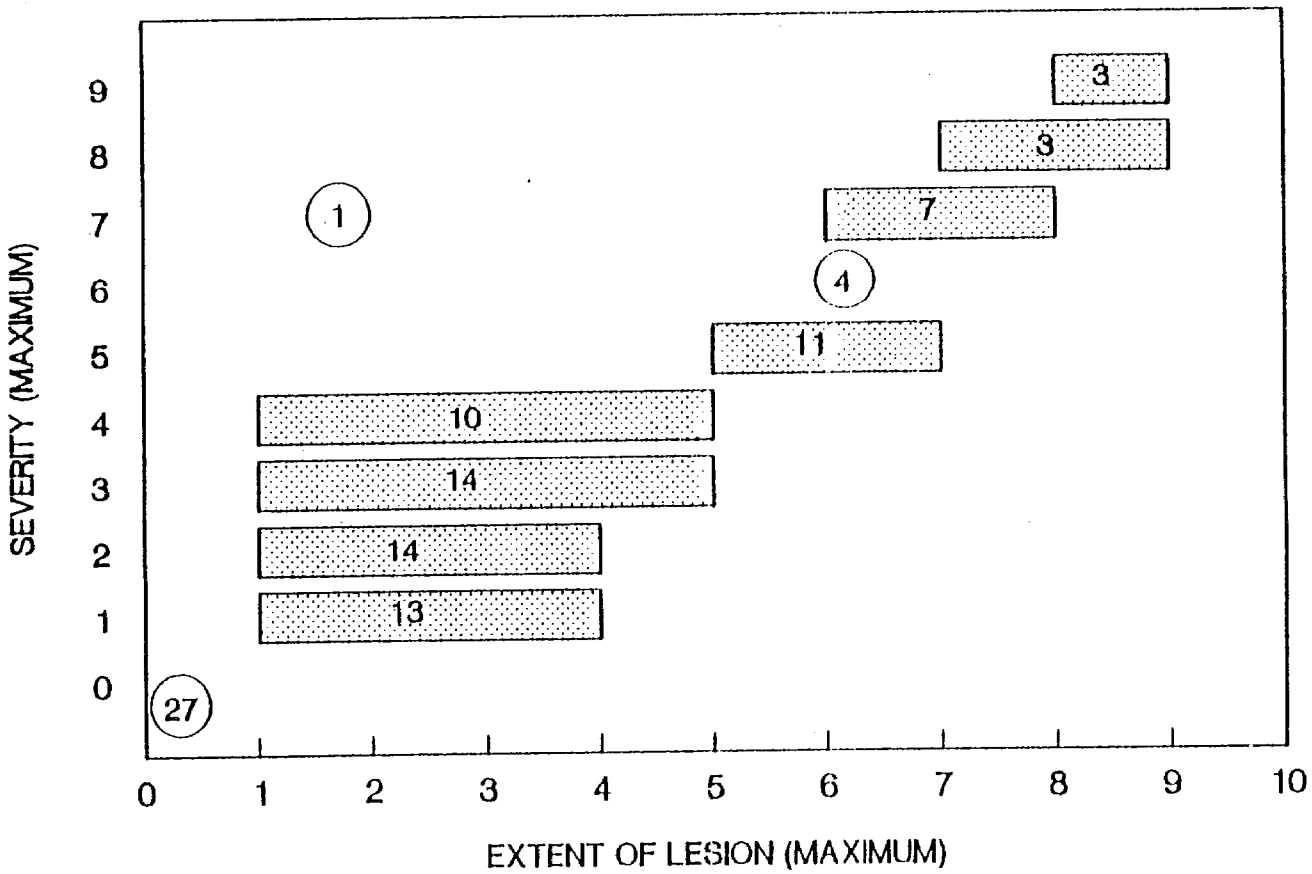


CHART 2

# CENTRIACINAR REGION DISEASE

n=107

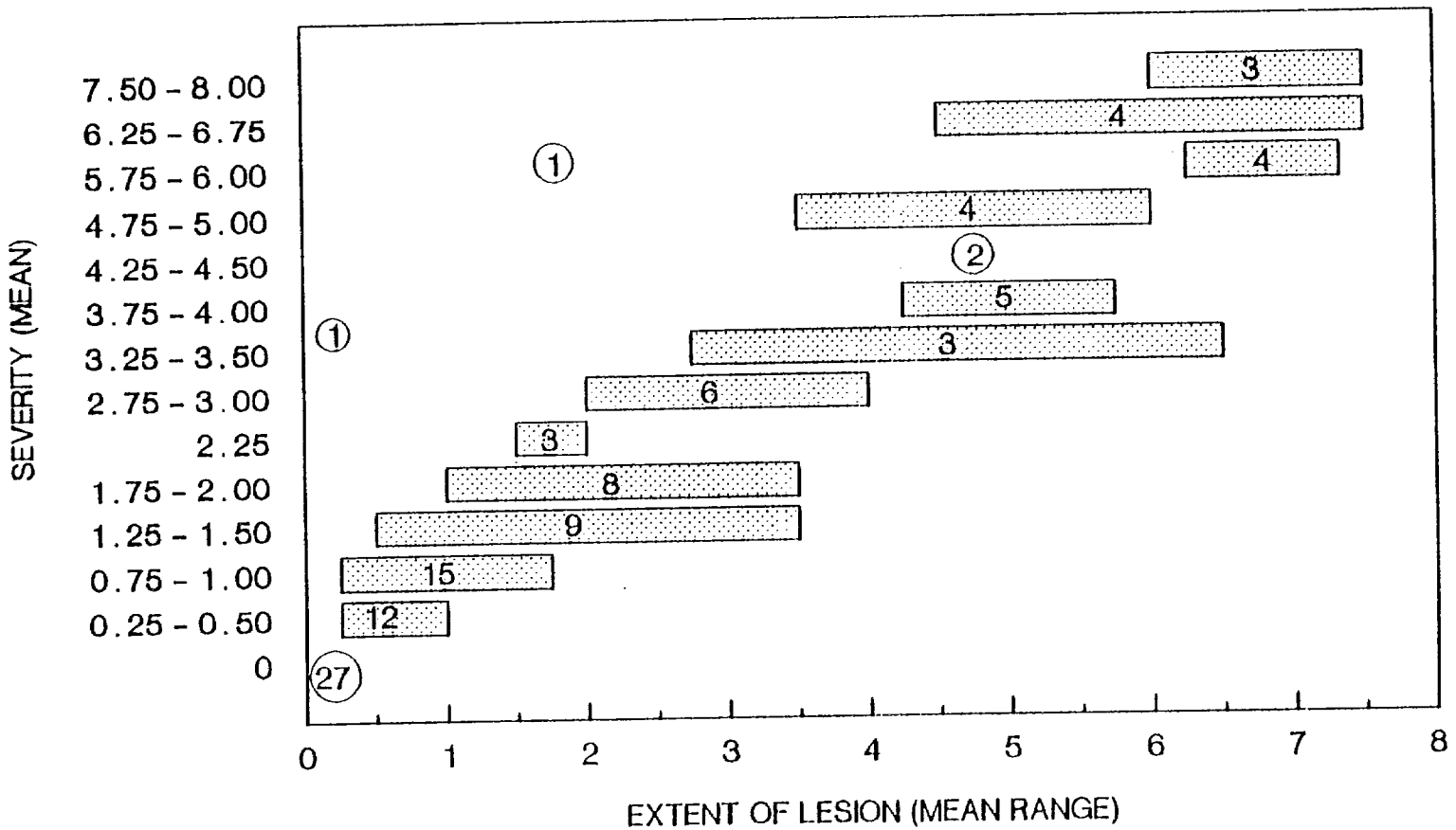


CHART 3

# CHRONIC BRONCHITIS

n=112

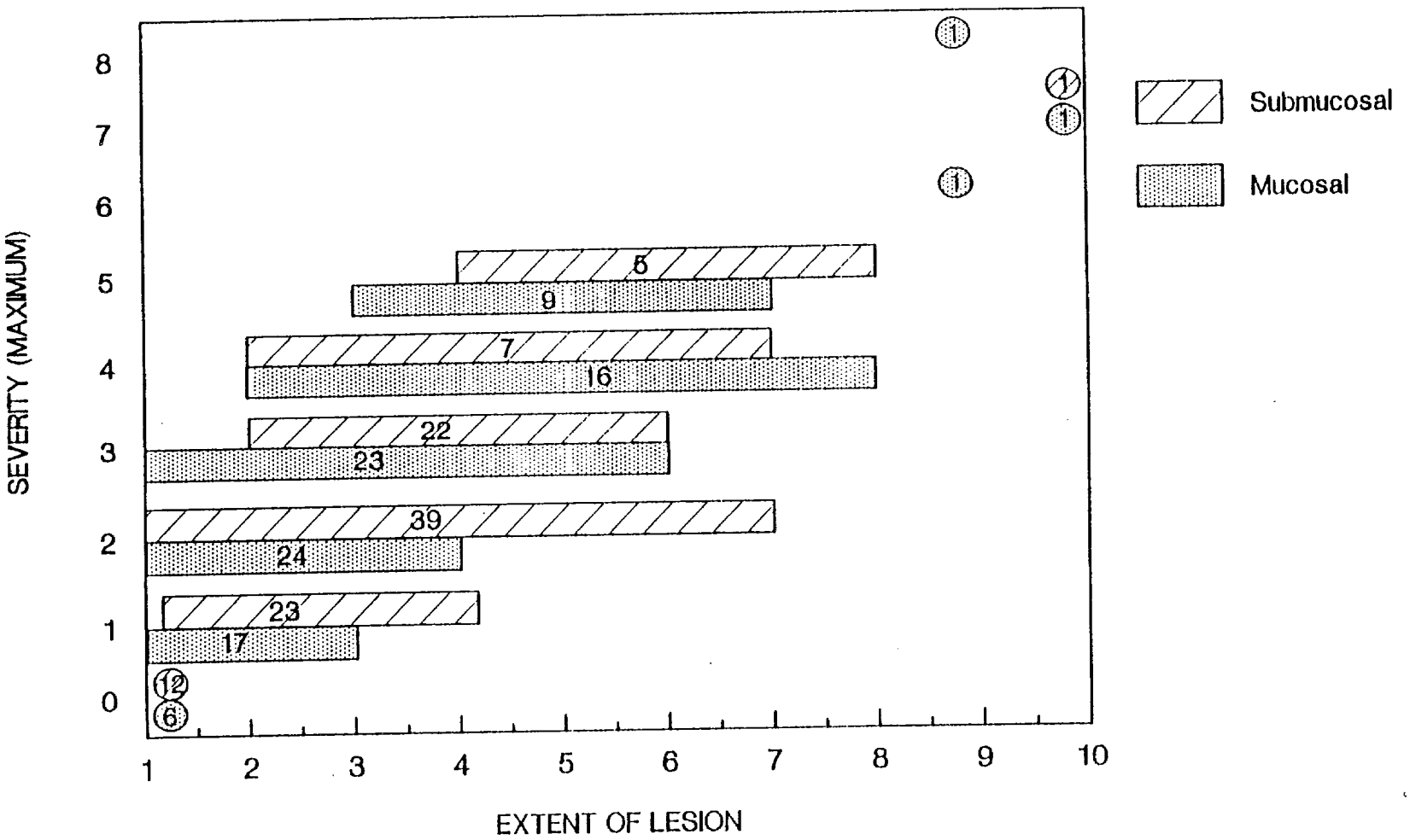
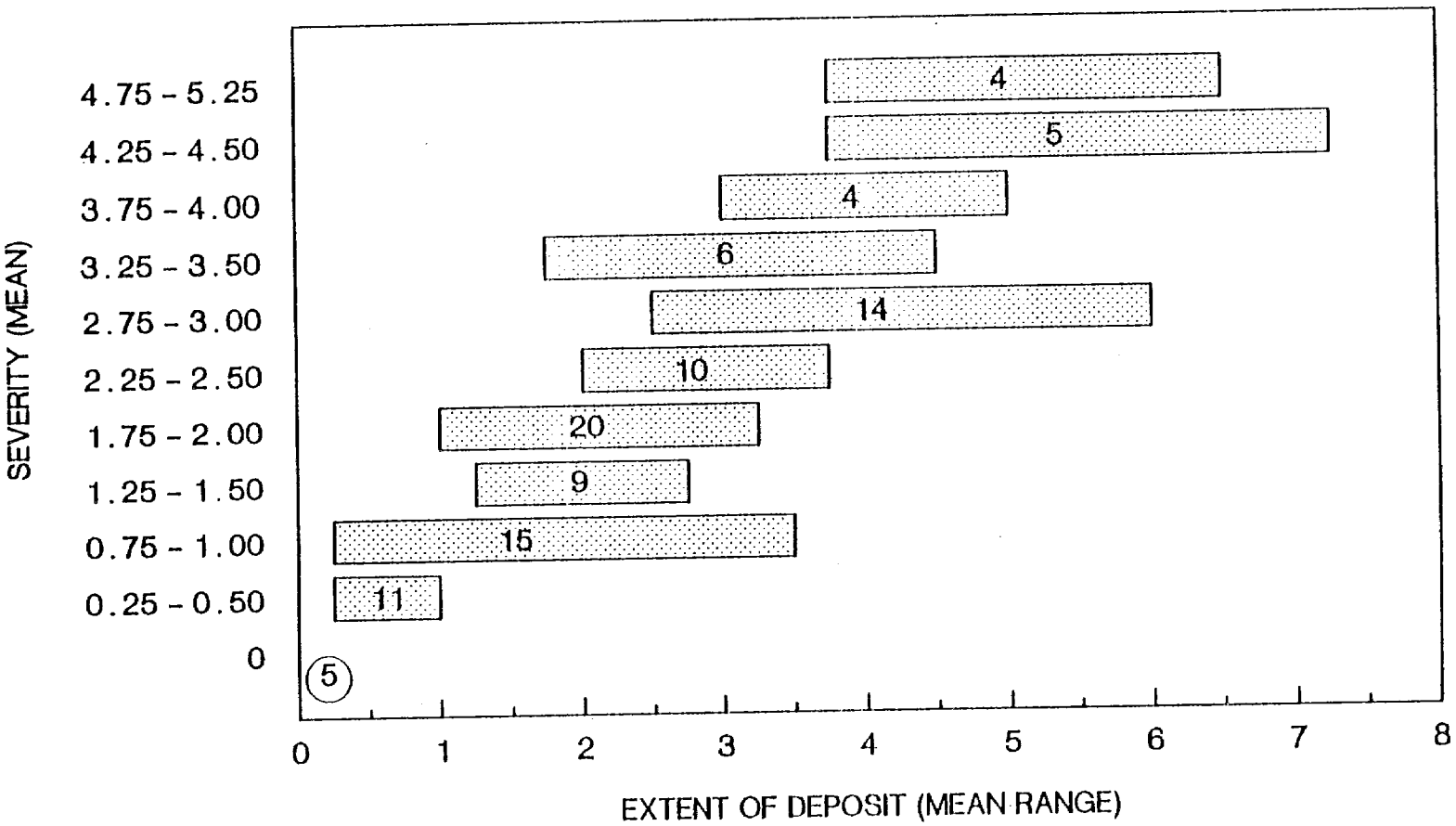


CHART 4

# ANTHRACOTIC PIGMENT

n=103



APPENDIX A

MEETINGS, PHONE CONFERENCES: May - September, 1987

1. **May 28, 1987**, USC School of Medicine

Participants: Roger Detels, Russell P. Sherwin and Dane Westerdahl

Agenda: Prelimary draft pertinent information to be included in the questionaire for the next of kin and also composition of letter requesting interview were discussed. Also details for the collection of lungs and epidemiologic data were defined.

2. **June 18, 1987**, UCLA.

Participants: Virginia Clark, Roger Detels, Russell P. Sherwin, Clifford Wang, Emilia Sanchez and Chaoke Liang.

Agenda: Discussion of criteria and approaches for the statistical evaluation of pathologic data and for coordination with the epidemiologic study were the main items on the agenda. The letter and questionaire prepared for interviewing the next of kin were reviewed.

3. **June 29, 1987**, Los Angeles County Coroner's Office and USC School of Medicine

Participants: Virginia Clark, Stan Dawson, Roger Detels, Russell P. Sherwin, Arnis Richters, Valda Richters, Dane Weterdahl, Karim Damji, Chaoke Liang, Emilia Sanchez, and Clifford Wang.

Agenda: The investigators were given a tour of the Coroner's Office and also met with the Coroner's Investigator Team to familiarize themselves with the information retrieving process.

4. **July 30. 1987**, Los Angeles County Coroner's Office

Participants: Roger Detels, Ronald Kornblum, Valda Richters, Russell P. Sherwin, Karim Damji, Chaoke Liang, Emilia Sanchez, and Clifford Wang.

Agenda: The letter and questionaire for next of kin were reviewed and minor modifications of the letter and the questionaire were made. Dr. Ronald Kornblum, the Deputy Chief Coroner, familiarized the investigators with the procedures and scheduling of daily autopsies. The procedure for obtaining lungs and data from the Investigator's Report were defined.

## LETTER TO BE SENT TO NEXT-OF-KIN

Dear _____,

Through the Los Angeles County Coroner's office, we have been informed of the sad loss of your _____. We know that you are still suffering from his/her loss, and we recognize the hardship you may be under. Perhaps, you would be willing, however, despite your terrible loss to help us to avoid similar trauma to other families by helping us to answer a few questions. They have to do with determining if changes in _____ lung's may have been related to exposure to air pollution.

We have been concerned that exposure to the types of air pollutants which are common in Southern California may be causing serious respiratory disease in people. Recent studies at UCLA have suggested that changes in the lung due to exposure to air pollution may begin before 25 years of age. Unfortunately identification of these early changes is difficult to measure using currently available tests of breathing ability. We must, therefore, examine lungs from people under twenty-five years to identify these early changes. We are cooperating with the Los Angeles County Coroner's Office to study the lungs of young people living in California who have died, to look for changes in their lungs which may have been due to exposure to air pollution. Autopsies are routinely performed on all fatal accident investigations as a matter of law and are not carried out specifically as part of this study.

One of our research associates can ask you these questions over the telephone in about 15-20 minutes. The questions he would ask about _____ may include the following:

respiratory conditions or diseases
personal habits (e.g.: smoking, drinking)
occupations and hobbies
places of schooling
places where _____ lived

We know that this is a difficult time for you, but your answers to these questions can help us to learn more about how air pollution causes respiratory disease and may ultimately help in preventing future residents of Southern California from suffering respiratory disease because of exposure to air pollution. You are under no obligation to participate in this study, and if you decide to participate, you may decline to answer any question. All information collected will be confidential. You will be called by telephone in approximately one week. At that time, you may decide to participate or not. If you prefer, you can contact us at (213) 206-3379 or write to us at the addresses below to indicate whether or not you wish to be called. If you have any questions about the study, please call us collect at (213) 206-3379 between 9 A.M. and 5 P.M.

Sincerely,

Russell Sherwin, MD
Professor of Pathology
USC School of Medicine
Department of Pathology, HMR-201
2011 Zonal Avenue
LA, CA 90033

Roger Detels, MD, MS
Professor of Epidemiology
School of Public Health
University of California, Los Angeles
LA, CA 90024

USC Autopsy Study

Dear _____,

We have been concerned that exposure to the types of air pollutants which are common in Southern California may be causing serious respiratory disease in people. Recent studies have suggested that changes in the lung due to exposure to air pollution may begin before 25 years of age. Unfortunately identification of these early changes is difficult to measure using tests of breathing ability. We must, therefore, examine lungs from people under twenty five to identify these early changes. We, in the Coroner's Office, are cooperating with the University of Southern California School of Medicine and the UCLA School of Public Health to study the lungs of young people living in Southern California who have died to see if we can identify changes in the lung due to exposure to air pollution.

We regret that your _____ passed away recently. We know that you are still suffering from his/her loss. We would, however, like to ask you a few questions about _____ which will help us determine if changes in _____'s lungs may have been related to exposure to air pollution. We can ask you these questions over the telephone in about 15 minutes. The questions we would ask about _____ may include the following:

respiratory conditions or diseases
personal habits (e.g.: smoking, drinking)
occupations and hobbies
places of schooling
places where _____ lived

We know that this is a difficult time for you, but your answers to these questions can help us to learn more about how air pollution causes respiratory disease and may ultimately help in preventing future residents of Southern California from suffering respiratory disease because of exposure to air pollution.

If you have any questions about the study or would prefer to call us, please call us collect at _____ between _____.

Thank you sincerely,

_____, Coroner

TABLE 16

INCIDENCE OF PATHOLOGICAL CHANGES OBSERVED
in
THE ABSENCE OF CENTRIACINAR REGION DISEASE
Total: 27 Cases

| Pathological Changes Observed | No Cases | Percent |
|---|---|---|
| Desquamative Interstitial Pneumonitis | 1 | 3% |
| Chronic Interstitial Pneumonitis | 5 | 18% |
| Chronic bronchiolitis | 7 | 25% |
| Peribronchiolar fibrosis | 1 | 3% |
| Centrilobular emphysema | 0 | 0% |
| Panlobular emphysema | 0 | 0% |

# PREAMBLE FOR THE QUESTIONAIRE

Hello, my name is Clifford Wang. I am a research associate at the UCLA School of Public Health. I am calling with regard to the letter sent to you by Russell Sherwin, M.D. and Roger Detels, M.D., M.S. concerning a study we are conducting on the effects of air pollution on the lungs of young adults. We know this is a difficult time for you and that you may still be suffering from the loss of your _____. However, this study can help us to better understand how air pollution causes respiratory disease and may ultimately help in preventing future residents of Southern California from suffering respiratory disease because of exposure to air pollution. Information about _____ can help us to determine if changes in _____'s lungs were related to exposure to air pollution. The questions we would ask about _____ include the following: residential history, occupation, education, hobbies, respiratory conditions or diseases, smoking, drinking, and possible drug use. The questionnaire takes approximately 15-20 minutes. All information will be kept confidential. You are under no obligation to participate, and you may decline to answer any question during the interview. If there is a more convenient time or place for you, an appointment can be set up. Have you understood everything so far? Would you like me to explain anything over or more thoroughly? Would you like to participate in this study?

If the answer is no: Do you know of anyone else who might provide this information on _____?

# AIR POLLUTION AND LUNG PATHOLOGY IN YOUNG ADULTS

## Questionnaire

2. ID NUMBER _____

3. SEX: Male _____ Female _____

4. BIRTHDATE: _____/_____/_____

5. RACE/ETHNICITY: _____

6. INFORMANT: Parent ____ Spouse ____ Guardian ____
Other Relative ____ Friend ____ Other ____

PREAMBLE: I AM NOW GOING TO ASK YOU SOME QUESTIONS ABOUT _____'S RESIDENCE HISTORY, OCCUPATION, EDUCATION, AND HOBBIES.

RESIDENTIAL HISTORY (including military service)

| 7. Residences (address/zip) | Census Tract | Length of Stay | From Age | To Age |
|---|---|---|---|---|
| (1) | | | | |
| (2) | | | | |
| (3) | | | | |
| (4) | | | | |
| (5) | | | | |
| (6) | | | | |

| | Energy Source for Cooking | Energy Source for Heating | Type of Heating System | Type of Air Conditioning |
|---|---|---|---|---|
| (1) | | | | |
| (2) | | | | |
| (3) | | | | |
| (4) | | | | |
| (5) | | | | |
| (6) | | | | |

OCCUPATION

8. Was _____ ever employed?

(1) Yes _____
(2) No _____
(99) Unknown _____

9. If no, was _____ a student, housewife, or unemployed?

(1) Student _____
(2) Housewife _____
(3) Unemployed _____
(99) Unknown _____

IF QUESTION 8 WAS ANSWERED NO OR UNKNOWN, SKIP TO QUESTION 13.

10. List all jobs starting with the most recent.

| Jobs | Hours/ Week | From Age | To Age | Address/ Zip Code | Census Tract |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

11. Was _____ exposed to any of the following at work?

(0) None _____
(1) Metals _____
(2) Pesticides _____
(4) Asbestos _____
(8) Powders _____
(16) Paints and solvents _____
(32) Gasoline/oils _____
(64) Plastics/fiberglass _____
(128) Crop dusts and sprays _____
(256) Wood shavings _____
(512) Other dust, fumes, or toxics _____
(999) Unknown _____
Total _____

12. Did _____ spend more time working indoors or outdoors?

(1) Outdoors _____
(2) Indoors _____
(99) Unknown _____

EDUCATION

13. What is the highest grade (or year) of regular school that _____ had completed?

(1) ≤ 8th grade _____
(2) High school _____
(3) College _____
(4) More than college _____
(99) Unknown _____

14. Where were the schools that _____ attended located?

| Location (address/zip code) | Census Tract | From Age | To Age |
|---|---|---|---|
| _____ | _____ | _____ | _____ |
| _____ | _____ | _____ | _____ |
| _____ | _____ | _____ | _____ |
| _____ | _____ | _____ | _____ |

15. What is the highest level of education attained by the parents?

(1) ≤ 8th grade _____
(2) High school _____
(3) College _____
(4) More than college _____
(99) Unknown _____

HOBBIES

16. Has _____ ever had or been exposed to any of the following hobbies?

(0) None _____
(1) Model building _____
(2) Bird breeding or handling _____
(4) Gem/stone cutting _____
(8) Woodworking _____
(16) Sculpturing _____
(32) Photography/film processing _____
(64) Painting _____
(128) Making surfboards or other fiberglass items _____
(999) Unknown _____
Total _____

PREAMBLE: I AM NOW GOING TO ASK YOU SOME QUESTIONS ABOUT _____'S RESPIRATORY CONDITIONS OR DISEASES.

COUGH

17. Did _____ have a chronic cough?

(1) Yes _____
(2) No _____
(99) Unknown _____

IF THE ANSWER IS NO OR UNKNOWN TO QUESTION 17, SKIP TO QUESTION 20.

18. How long had he/she had that cough? _____ yrs.

19. Was this a productive cough (phlegm, mucus, or sputum brought up)?

(1) Yes _____
(2) No _____
(99) Unknown _____

WHEEZING

20. Did _____'s breathing ever sound wheezing or whistling?

(1) Yes _____
(2) No _____
(99) Unknown _____

BREATHLESSNESS

21. Was _____ troubled by shortness of breath when hurrying on level ground or walking up a slight hill?

(1) Yes _____
(2) No _____
(99) Unknown _____

22. Did _____ suddenly become short of breath when taking it easy (not exercising)?

(1) Yes _____
(2) No _____
(99) Unknown _____

CHEST ILLNESS

23. Did a physician ever diagnose _____ as having the following chronic conditions?

(0) None _____
(1) Asthma _____
(2) Chronic Bronchitis _____
(4) Emphysema _____
(8) Tuberculosis _____
(16) Heart disease _____
(88) Other _____
(99) Unknown _____
Total _____

24. Did _____ ever have the following acute conditions?

| | | |
|---|---|---|
| (0) | None | ____ |
| (1) | Pneumonia | ____ |
| (2) | Frequent chest colds | ____ |
| (4) | Collapsed lung | ____ |
| (8) | Tuberculosis | ____ |
| (16) | Heart condition | ____ |
| (88) | Other | ____ |
| (99) | Unknown | ____ |
| | Total | ____ |

IF THE ANSWER IS NONE OR UNKNOWN FOR QUESTION 23 AND 24, SKIP TO QUESTION 29.

25. What level of restriction did these diseases cause?

(0) None
(1) Limited physical activity
(2) Restricted from work or study
(3) No physical activity
(4) Confined to chair or bed
(99) Unknown

| Condition/Disease | Level of Restriction |
|---|---|
| A. Chronic ____ | ____ |
| B. Acute ____ | ____ |

26. Has _____ ever been hospitalized for any respiratory condition?

| | |
|---|---|
| (1) Yes | ____ |
| (2) No | ____ |
| (99) Unknown | ____ |

27. If yes, which condition?

A. Chronic

| | | |
|---|---|---|
| (0) | None | ____ |
| (1) | Asthma | ____ |
| (2) | Chronic bronchitis | ____ |
| (4) | Emphysema | ____ |
| (8) | Tuberculosis | ____ |
| (16) | Other | ____ |
| (99) | Unknown | ____ |
| | Total | ____ |

B. Acute

(0) None _____
(1) Pneumonia _____
(2) Frequent chest colds _____
(4) Collapsed lung _____
(8) Acute bronchitis _____
(16) Other _____
(99) Unknown _____
Total _____

28. Did _____ ever take prescribed medication for any chronic or persistent respiratory, heart, or neurological conditions?

| Respiratory | Cardiovascular | Neurological |
|---|---|---|
| _____ | _____ | _____ |
| _____ | _____ | _____ |
| _____ | _____ | _____ |
| _____ | _____ | _____ |
| _____ | _____ | _____ |

PREAMBLE: I AM NOW GOING TO ASK YOU SOME QUESTIONS ABOUT _____'S SMOKING HABITS, ALCOHOL CONSUMPTION, AND DRUG USE.

SMOKING

29. Did _____ smoke cigarettes regularly, occasionally, or never?

(1) Regularly _____
(2) Occasionally _____
(3) Never _____
(99) Unknown _____

IF THE ANSWER TO QUESTION 29 IS NEVER OR UNKNOWN, THEN SKIP TO QUESTION 37.

30. About how many cigarettes did _____ usually smoke each day?

(1) < 1/2 Pack _____
(2) 1/2 Pack to 1 Pack _____
(3) > 1 Pack _____
(99) Unknown _____

31. When did _____ begin to smoke cigarettes?

(1) Before age 15 _____
(2) Age 15 to 20 _____
(3) Age 21 to 25 _____
(99) Unknown _____

32. Was _____ smoking until he/she died?

(1) Yes _____
(2) No _____
(99) Unknown _____

33. If no, then when did _____ stop smoking? age _____

34. Was this influenced by having a cough, wheezing, or shortness of breath?

(1) Yes _____
(2) No _____
(99) Unknown _____

35. Did _____ ever smoke anything other than cigarettes?

(0) None _____
(1) Pipes _____
(2) Cigars _____
(4) Marijuana _____
(8) Other _____
(99) Unknown _____

36. If yes, for how long? _____ yrs.

37. In _____'s household, has anyone else ever smoked?

(1) Yes _____
(2) No _____
(99) Unknown _____

IF THE ANSWER TO QUESTION 37 IS NO OR UNKNOWN, SKIP TO QUESTION 39.

38. What is the relationship of the smoker(s) to _____?

(1) Mother _____
(2) Father _____
(4) Spouse _____
(8) Brother/sister _____
(16) Other relative/friend _____
(99) Unknown _____
Total _____

ALCOHOL

39. Did _____ drink any alcoholic beverages?

(1) Yes _____
(2) No _____
(99) Unknown _____

IF THE ANSWER TO QUESTION 39 IS NO OR UNKNOWN, SKIP TO QUESTION 43.

40. If yes, how many bottles or cans of beer per week? _____ bottles/cans

41. If yes, how many glasses of wine per week? _____ glasses

42. If yes, how much hard liquor per week? _____ drinks

DRUG USE

43. Did _____ ever use drugs?

(1) Yes _____
(2) No _____
(99) Unknown _____

IF THE ANSWER TO QUESTION 43 IS NO OR UNKNOWN, STOP HERE.

44. Did _____ ever use any of the following drugs?

(0) None _____
(1) Cocaine _____
(2) Amphetamines _____
(4) Heroin/morphine _____
(8) PCP/Angel's dust _____
(16) Tramquilizers _____
(88) Other _____
(99) Unknown _____

45. Did _____ use these drugs regularly or occasionally?

(1) Regularly
(2) Occasionally
(99) Unknown

| Drugs | Level of Usage |
|---|---|
| (1) Cocaine | _____ |
| (2) Amphetamines | _____ |
| (3) Heroin/morphine | _____ |
| (4) PCP/ Angel's dust | _____ |
| (5) Tranquilizers | _____ |

STOP HERE. THIS IS THE END OF THE QUESTIONNAIRE.

# AIR POLLUTION AND LUNG PATHOLOGY CODING SHEET

2. ID NUMBER ___ ___ ___ ___ ___

3. SEX ___

4. BIRTHDATE ___ ___ / ___ ___ / ___ ___

5. RACE ___

6. INFORMANT ___

7. RESIDENTIAL HISTORY

| | | | |
|---|---|---|---|
| CENSUS TRACT | ___ ___ ___ ___ | ___ ___ ___ ___ | ___ ___ ___ ___ |
| LENGTH | ___ ___ | ___ ___ | ___ ___ |
| FR_AGE | ___ ___ | ___ ___ | ___ ___ |
| TO_AGE | ___ ___ | ___ ___ | ___ ___ |
| COOKING ENERGY | ___ | ___ | ___ |
| HEATING ENERGY | ___ | ___ | ___ |
| HEATING SYSTEM | ___ | ___ | ___ |
| AIR CONDITION | ___ | ___ | ___ |

8. EMPLOYMENT ___ ___

9. STUDENT/ HOUSEWIFE ___ ___

| | | | |
|---|---|---|---|
| 10. JOBS | ___ ___ | ___ ___ | ___ ___ |
| HRS/WK | ___ ___ | ___ ___ | ___ ___ |
| FR_AGE | ___ ___ | ___ ___ | ___ ___ |
| TO_AGE | ___ ___ | ___ ___ | ___ ___ |
| CENSUS TRACT | ___ ___ ___ ___ | ___ ___ ___ ___ | ___ ___ ___ ___ |

11. OCCUPATION ___ ___ ___

12. INDOOR/
OUTDOOR ___ ___

13. EDUCATION ___ ___

14. CENSUS
TRACT ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

FR_AGE ___ ___ ___ ___ ___ ___

TO_AGE ___ ___ ___ ___ ___ ___

15. PARENTS
EDUCATION ___ ___

16. HOBBIES ___ ___ ___

17. COUGH ___ ___

18. LENGTH ___ ___

19. MUCUS ___ ___

20. WHEEZING ___ ___

21. SHORTNESS
OF BREATH ___ ___

22. BREATHLESS ___ ___

23. CHRONIC ___ ___

24. ACUTE ___ ___

25. LEVEL OF
RESTRICT ___ ___ ___

26. HOSPITAL ___ ___

27. CHRONIC
HOSP ___ ___ ___

ACUTE
HOSP ___ ___ ___

28. RESPIRATORY ___ ___ ___ ___ ___ ___

CARDIOVASCULAR ___ ___ ___ ___ ___ ___

NEUROLOGICAL ___ ___ ___ ___ ___ ___

29. SMOKING ___ ___

30. PACK ___ ___

31. BEGIN AGE ___ ___

32. SMOKING UNTIL DEATH ___ ___

33. AGE STOP ___ ___

35. SMOKE OTHER ___ ___

36. PERIOD ___ ___

37. HOUSEHOLD SMOKERS ___ ___

38. RELATION ___ ___

39. ALCOHOL ___ ___

40. BEER ___ ___

41. WINE ___ ___

42. LIQUOR ___ ___

43. DRUG USE ___ ___

44. TYPES OF DRUGS ___ ___

45. FREQUENCY

COCAINE ___ ___

AMPHETAMINES ___ ___

HEROIN/MORPH ___ ___

PCP ___ ___

TRANQUIL ___ ___

July 1987 Revision

# AIR POLLUTION AND LUNG PATHOLOGY IN YOUNG ADULTS

## Questionnaire

1. NAME _____

2. ID NUMBER _____

3. SEX: Male _____ Female _____

4. BIRTHDATE: _____/_____/_____

5. RACE/ETHNICITY: _____

6. INFORMANT: Parent ____ Spouse ____ Guardian ____
Other Relative ____ Friend ____ Other ____

PREAMBLE: I AM NOW GOING TO ASK YOU SOME QUESTIONS ABOUT _____'S RESIDENCE HISTORY, OCCUPATION, EDUCATION, AND HOBBIES.

RESIDENTIAL HISTORY (including military service)

| 7. Residences (address/zip) | Census Tract | Length of Stay | From Age | To Age |
|---|---|---|---|---|
| (1) | | | | |
| (2) | | | | |
| (3) | | | | |
| (4) | | | | |
| (5) | | | | |
| (6) | | | | |

| | Energy Source for Cooking | Energy Source for Heating | Type of Heating System | Type of Air Conditioning |
|---|---|---|---|---|
| (1) | | | | |
| (2) | | | | |
| (3) | | | | |
| (4) | | | | |
| (5) | | | | |
| (6) | | | | |

OCCUPATION

8. Was _____ ever employed?

(1) Yes _____
(2) No _____
(99) Unknown _____

9. If no, was _____ a student, housewife, or unemployed?

(1) Student _____
(2) Housewife _____
(3) Unemployed _____
(99) Unknown _____

IF QUESTION 8 WAS ANSWERED NO OR UNKNOWN, SKIP TO QUESTION 13.

10. List all jobs starting with the most recent.

| Jobs | Hours/ Week | From Age | To Age | Address/ Zip Code | Census Tract |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

11. Was _____ exposed to any of the following at work?

(0) None _____
(1) Metals _____
(2) Pesticides _____
(4) Asbestos _____
(8) Powders _____
(16) Paints and solvents _____
(32) Gasoline/oils _____
(64) Plastics/fiberglass _____
(128) Crop dusts and sprays _____
(256) Wood shavings _____
(512) Other dust _____
(999) Unknown _____
Total _____

12. Did _____ spend more time working indoors or outdoors?

(1) Outdoors _____
(2) Indoors _____
(99) Unknown _____

EDUCATION

13. What is the highest grade (or year) of regular school that _____ had completed?

(1) ≤ 8th grade _____
(2) High school _____
(3) College _____
(4) More than college _____
(99) Unknown _____

14. Where were the schools that _____ attended located?

| Location (address/zip code) | Census Tract | From Age | To Age |
|---|---|---|---|
| _____ | _____ | _____ | _____ |
| _____ | _____ | _____ | _____ |
| _____ | _____ | _____ | _____ |
| _____ | _____ | _____ | _____ |

15. What is the highest level of education attained by the parents?

(1) ≤ 8th grade _____
(2) High school _____
(3) College _____
(4) More than college _____
(99) Unknown _____

HOBBIES

16. Has _____ ever had any of the following hobbies?

| | | |
|---|---|---|
| (0) | None | _____ |
| (1) | Model building | _____ |
| (2) | Bird breeding or handling | _____ |
| (4) | Gem/stone cutting | _____ |
| (8) | Woodworking | _____ |
| (16) | Sculpturing | _____ |
| (32) | Photography/film processing | _____ |
| (64) | Painting | _____ |
| (128) | Making surfboards or other fiberglass items | _____ |
| (999) | Unknown | _____ |
| | Total | _____ |

PREAMBLE: I AM NOW GOING TO ASK YOU SOME QUESTIONS ABOUT _____'S RESPIRATORY CONDITIONS OR DISEASES.

COUGH

17. Did _____ have a chronic cough?

(1) Yes _____
(2) No _____
(99) Unknown _____

IF THE ANSWER IS NO OR UNKNOWN TO QUESTION 17, SKIP TO QUESTION 20.

18. How long had he/she had that cough? _____ yrs.

19. Was this a productive cough (phlegm, mucus, or sputum brougnt up)?

(1) Yes _____
(2) No _____
(99) Unknown _____

WHEEZING

20. Did _____'s breathing ever sound wheezing or whistling?

(1) Yes _____
(2) No _____
(99) Unknown _____

BREATHLESSNESS

21. Was _____ troubled by shortness of breath when hurrying on level ground or walking up a slight hill?

(1) Yes _____
(2) No _____
(99) Unknown _____

22. Did _____ suddenly become short of breath when taking it easy (not exercising)?

(1) Yes _____
(2) No _____
(99) Unknown _____

CHEST ILLNESS

23. Did a physician ever diagnose _____ as having the following chronic conditions?

(0) None _____
(1) Asthma _____
(2) Chronic Bronchitis _____
(4) Emphysema _____
(8) Tuberculosis _____
(99) Unknown _____
Total _____

24. Did _____ ever have the following acute conditions?

| | | |
|---|---|---|
| (0) | None | ____ |
| (1) | Pneumonia | ____ |
| (2) | Frequent chest colds | ____ |
| (4) | Collapsed lung | ____ |
| (8) | Tuberculosis | ____ |
| (99) | Unknown | ____ |
| | Total | ____ |

IF THE ANSWER IS NONE OR UNKNOWN FOR QUESTION 23 AND 24, SKIP TO QUESTION 29.

25. What level of restriction did these diseases cause?

(0) None
(1) Limited physical activity
(2) Restricted from work or study
(3) No physical activity
(4) Confined to chair or bed
(99) Unknown

| Condition/Disease | Level of Restriction |
|---|---|
| A. Chronic ____ | ____ |
| B. Acute ____ | ____ |

26. Has _____ ever been hospitalized for any respiratory condition?

| | |
|---|---|
| (1) Yes | ____ |
| (2) No | ____ |
| (99) Unknown | ____ |

27. If yes, which condition?

A. Chronic

| | | |
|---|---|---|
| (0) | None | ____ |
| (1) | Asthma | ____ |
| (2) | Chronic bronchitis | ____ |
| (4) | Emphysema | ____ |
| (8) | Tuberculosis | ____ |
| (16) | Other | ____ |
| (99) | Unknown | ____ |
| | Total | ____ |

B. Acute

(0) None _____
(1) Pneumonia _____
(2) Frequent chest colds _____
(4) Collapsed lung _____
(8) Acute bronchitis _____
(16) Other _____
(99) Unknown _____
Total _____

28. Did _____ ever take prescribed medication for any chronic or persistent respiratory or heart conditions?

| Respiratory/Medication | Cardiovascular/Medication |
|---|---|
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |

PREAMBLE: I AM NOW GOING TO ASK YOU SOME QUESTIONS ABOUT _____'S SMOKING HABITS, ALCOHOL CONSUMPTION, AND DRUG USE.

SMOKING

29. Did _____ smoke cigarettes regularly, occasionally, or never?

(1) Regularly _____
(2) Occasionally _____
(3) Never _____
(99) Unknown _____

IF THE ANSWER TO QUESTION 29 IS NEVER OR UNKNOWN, THEN SKIP TO QUESTION 37.

30. About how many cigarettes did _____ usually smoke each day?

(1) < 1/2 Pack _____
(2) 1/2 Pack to 1 Pack _____
(3) > 1 Pack _____
(99) Unknown _____

31. When did _____ begin to smoke cigarettes?

(1) Before age 15 _____
(2) Age 15 to 20 _____
(3) Age 21 to 25 _____
(99) Unknown _____

32. Was _____ smoking until he/she died?

(1) Yes _____
(2) No _____
(99) Unknown _____

33. If no, then when did _____ stop smoking? age _____

34. Was this influenced by having a cough, wheezing, or shortness of breath?

(1) Yes _____
(2) No _____
(99) Unknown _____

35. Did _____ ever smoke anything other than cigarettes?

(0) None _____
(1) Pipes _____
(2) Cigars _____
(4) Marijuana _____
(8) Other _____
(99) Unknown _____

36. If yes, for how long? _____ yrs.

37. In _____'s household, has anyone else ever smoked?

(1) Yes _____
(2) No _____
(99) Unknown _____

IF THE ANSWER TO QUESTION 37 IS NO OR UNKNOWN, SKIP TO QUESTION 39.

38. What is the relationship of _____ with the smoker(s)?

(1) Mother _____
(2) Father _____
(4) Spouse _____
(8) Brother/sister _____
(16) Other relative/friend _____
(99) Unknown _____
Total _____

ALCOHOL

39. Did _____ drink any alcoholic beverages?

(1) Yes _____
(2) No _____
(99) Unknown _____

IF THE ANSWER TO QUESTION 39 IS NO OR UNKNOWN, SKIP TO QUESTION 43.

40. If yes, how many bottles or cans of beer per week? _____ bottles/cans

41. If yes, how many glasses of wine per week? _____ glasses

42. If yes, how much hard liquor per week? _____ drinks

DRUG USE

43. Did _____ ever use any of the following drugs?

(0) None _____
(1) Cocaine _____
(2) Amphetamines _____
(4) Heroin/morphine _____
(99) Unknown _____

IF THE ANSWER TO QUESTION 43 IS NONE OR UNKNOWN, STOP.

44. Did _____ use these drugs regularly or occasionally?

(1) Regularly
(2) Occasionally
(99) Unknown

| Drugs | Level of Usage |
|---|---|
| (1) Cocaine | _____ |
| (2) Amphetamines | _____ |
| (3) Heroin/morphine | _____ |

# AIR POLLUTION AND LUNG PATHOLOGY STUDY

## Instructions for Interviewers

QUESTION 5.

There are five possible answers for this question:
(1) White
(2) Black
(3) Spanish surname
(4) Asian / Pacific Islander
(5) Other

QUESTION 7.

Energy Source for Cooking: electric, natural gas, propane gas, coal, wood.
Energy Source for Heating: electric. gas, solar, other.
Type of Heating System: forced air, floor furnace, radiator, electric coils, other.
Air conditioning: air conditioners, swamp coolers, humidifiers.

QUESTION 13.

High school includes 9th to 12th grade.
College: junior or community college, university.
More than college: graduate or professional school (law, medicine, business, etc.).

QUESTION 17.

A chronic cough is defined as "coughing for at least three months out of a year."

QUESTION 18.

Code an unknown with a 99 in the space.
If question 17 was answered no or unknown, then code question 18 and 19 as not applicable (N/A = 88).

QUESTION 19.

Phlegm: cloudy, viscid fluid (thick spit).
Mucus: clear, viscid fluid.
Sputum: expectorated matter (green, red, opaque, clear).

QUESTION 20.

Wheezing: a puffing sound.
Whistling: a sharp, shrill sound.

QUESTION 21.

Shortness of breath: tachypnea (i.e.: the breathing pattern you experience when you run as fast as you can and you suddenly stop).

QUESTION 23.

Definitions:

Asthma: a condition marked by continuous labored breathing accompanied by wheezing, by the sense of constriction in the chest and often by attacks of coughing or gasping.

Chronic bronchitis: condition associated with excessive tracheobronchial mucus production sufficient to cause cough with expectoration for at least three months of the year for more than two consecutive years

Emphysema: inspiration is normal but forced expiration is difficult. This is more prevalent when moving about.

Tuberculosis: some of its symptoms are chronic cough with sputum usually scanty and nonpurulent. Blood is often found in the sputum.

Coding:

Add each of the values checked off. Since each category has a value that is unique, the total value can be reached only one way. This allows us to consider multiple combinations of categories.

QUESTION 24.

Definitions:

Pneumonia: acute infectious disease. Various combinations of cough, fever, chest pain, difficult breathing, and production of sputum which may be mucoid, purulent, or bloody.

Cold: runny nose, sneezing, nasal congestion, sore throat, malaise, headache. Fever is unusual. In children: lower respiratory tract involvement may be seen including bronchitis, bronchiolitis and bronchopneumonia.

Pneumothorax: collapsed lung. Sudden pleuritic chest pain and difficult breathing.

Coding:

Same as in question 23.

QUESTION 25.

Definitions:

Limited physical activity: not limited in regular work activities, but limited in other activities such as church, clubs, hobbies, civic projects, sports, or games. Can work regularly but can only do light work.

Restricted physical activity: can perform activity at slow pace or infrequently. Can work regularly but needs frequent rests or other special conditions. Cannot go to school full-time or for long periods of time.
No physical activity: must stay in the house all or most of the time. inability to go to school, work at job or business.

Coding:
This question should be answered in two parts, (a) chronic and (b) acute. Each of these categories will be given a level of restriction and coded separately.

QUESTION 27.
This question is also broken into two parts, chronic and acute. Code as in question 23.

QUESTION 28.
Write in the condition and medication of the case. If the information is unknown, write 99 on the line.

QUESTION 29.
Regular is defined as "more than one cigarette per day."
Occasionally is defined as "less than one cigarette per day."

QUESTION 34.
A yes answer indicates that coughing, wheezing, or shortness of breath affected whether this person stopped smoking.

QUESTION 40 TO 42.
If unknown, code 99 in the space.

APPENDIX B

MEETINGS, PHONE CONFERENCES: October - December, 1987

1. **October 29, 1987**, USC School of Medicine

Participants: Ronald Kornblum, Arnis Richters and Russell P. Sherwin

Agenda: A meeting was held on this date to evaluate the progress of the project and in particular to facilitate the acquisition of appropriate pathologic materials from the Coroner's Office. It was agreed to continue with the protocol initiated with the recommendation that the burden placed on the pathologist performing the autopsy be minimized. In the latter respect, a meeting of Dr. Sherwin with the staff pathologists was proposed for the next staff conference, at which time Dr. Sherwin would present an outline of the project and ask for suggestions on organ procurement. In addition, the discussion considered means of retrieving demographic data from the records of the investigative team headed by Mr. Steven Dowell with a minimum of burden on their work schedule.

2. **November 4, 1987**, Los Angeles County Coroner's Office

At the regular staff meeting of the deputy coroners, Dr. Sherwin was afforded time on the agenda to present the needs of the project and to discuss the interactions required. Following the presentation, the questions asked indicated that cooperation would be very good and a plan on arranging for the specimens was formulated, i.e. determining suitability of specimen, time of acquisition, specimen handling (with necessary health precautions), and report of our findings.

3. **December 2, 1987**, Los Angeles County Coroner's Office

Participants: Steve Dowell, Russell P. Sherwin and Clifford Wang

Agenda: Since the initial mailing to the next of kin encountered difficulties related to the records of the Coroner's Office, Dr. Sherwin and Mr. Cliff Wang, the UCLA demographic data coordinator, met with Mr. Steven Dowell to revise the overall liaison plan. Mr. Dowell agreed to provide a confirmed listing of cases appropriate for follow up rather than to rely on the data obtained at the time of the autopsy.

A number of meetings were held by Dr. Sherwin with the Deputy Coroners and Chief of the Forensic Division, Dr. Joseph Choi, as part of the daily tissue acquisition carried out by Dr. Sherwin each morning. The purpose was to facilitate the acquisition of materials, establish criteria for suitability of case material, and offer consultant service.

Also, a number of phone conferences were held with Mr. Clifford Wang and with Dr. Roger Detels during the months of October through December. The calls primarily served to discuss the best means of initiating the next of kin contacts. Mr. Steven Dowell agreed to be the main liaison for Mr. Wang, i.e. they would exchange lists of cases, the former providing a list of case numbers and the latter the data pertaining to the case list. Dr. Sherwin's personnel are responsible for defining the case list and then mailing it to Mr. Wang.

APPENDIX C

MEETINGS, PHONE CONFERENCES: January - March, 1988

1. **January - March, 1988**

Telephone and formal conferences were held by Dr. Sherwin with Mr. Steve Dowell of the Coroner's office. The goal of the discussions was to establish a questionaire to be filled in by Coroner investigators and detective outside of the Coroner's office. Prototype questinaires were developed and reviewed in cooperaton with Dr. Roger Detels.

# AIR POLLUTION AND LUNG PATHOLOGY IN YOUNG ADULTS

Sex: male_____, female_____

Birthdate:_____/_____/_____

Race/ethnicity:_____

Informant: mother_____father_____Guardian_____other relative_____

friend_____other_____

Residential History (including military service):

Residences (address/zip code)

1._____

2._____

3._____

4._____

5._____

6._____

Was _____ever employed? yes_____,no_____unknown_____

If no, was _____a student_____housewife_____unemployed_____

If employed list all jobs starting with the most recent:

1._____

2._____

3._____

4._____

Was _____ever exposed to any of the following at work:

pesticides_____
asbestos_____
paints and solvents_____
gasoline_____
plastics/fiberglass_____
crop dusts and sprays_____
wood shavings_____
other dust, fumes, or toxic substances (please specify)_____
NO_____

Has _____ever been exposed to any of the following hobbies?

model building_____
bird breeding or handling_____
gem stone cutting or polishing_____
wood working_____
sculpturing_____
film processing/developing_____
painting_____
making surfboards or other fiberglass items
NO_____

Did a physician ever diagnose _____as having any of the following chronic conditions?

asthma_____
chronic bronchitis_____
emphysema_____
tuberculosis_____
heart disease_____
NO_____

If yes has _____ever been hospitalized for one of the conditions
no_____
yes_____ which ones?_____

Did _____ever have any of the following acute conditions?

pneumonia_____
frequent chest colds_____
collapsed lung_____
tuberculosis_____
acute bronchitis_____

Did _____ever take prescribed medication for any chronic or persistent respiratory, heart or neurologic condition?

NO_____

yes_____, please give name of drug and condition for which prescribed

_____

_____

_____

_____

Did _____smoke cigarettes regularly_____,occasionally_____never_____ unknown_____?

Did _____ever smoke anything other than cigarettes?

pipe_____

cigars_____

marijuana_____

APPENDIX D

MEETINGS, PHONE CONFERENCES: April - July, 1988

1. **April 22, 1988**, USC School of Medicine

Participants: Roger Detels, Raymond Neutra, Russell Sherwin, Arnis Richters, Valda Richters, and Clifford Wang.

The meeting was held to evaluate the progress of the project and to finalize the questionaire that will provide the basic information for the epidemiological evaluation.

The agenda included:

a. Dr. Sherwin's report on: (1) interactions and meetings with medical personnel at the Coroner's Office, i.e. Dr. Ronald Kornblum and Deputy Coroners; ; 2) status of availability of lung specimens, (3) results of meetings with Mr. Steven Dowell (liaison for interactions with staff and outside investigators); and 4) results of direct discussions with individual staff and outside investigators;

b. The protocol format for the retrieval of historical data;

Additional meetings were help with Mr. Cliff Wang and Mr. Steven Dowell on questionnaire and historical data collection, and in May Dr. Sherwin met with Mr. Dowell to discuss the progress of the data collection.

Name: _____ ID# _____

1. From Year To Year

Last Residence _____ ____ ____
Address

_____
City State Zip Code

Prior Residence(s) _____ ____ ____
Address

_____
City State Zip Code

_____ ____ ____
Address

_____
City State Zip Code

If a complete address cannot be obtained, ask for the cross street and any other information which might identify the residence.

2. Cigarette smoking
(1) Yes ____
(2) No ____
(9) Unknown ____

If yes:

| Amount Smoked | | #Years |
|---|---|---|
| (1) ≤ 1 pack/day | ____ | _____ |
| (2) > 1 pack/day | ____ | _____ |
| (3) Unknown | ____ | |

3. Marijuana smoking
(1) Yes ____
(2) No ____
(9) Unknown ____

If yes:

| Amount Smoked | | #Years |
|---|---|---|
| (1) ≤ 5 joint/wk | ____ | _____ |
| (2) > 5 joint/wk | ____ | _____ |
| (9) Unknown | ____ | |

4. Asthma
(1) Yes ____
(2) No ____
(9) Unknown ____

If yes, since what age? _____

5. Type of death
(1) Accident ____
(2) Homicide ____
(9) Unknown ____

If homicide:
(1) Gang related ____
(2) Innocent bystander ____
(3) Lover altercation ____
(4) Family altercation ____
(5) Other (indicate) ____ _____
(9) Unknown ____

Autopsy Information

1. Date of Death ___/___/___

2. Date of Autopsy ___/___/___

3. Needle Tracks
   (1) Yes ____
   (2) No ____
   (3) Not examined ____

4. Nose lesions indicative of smoking
   (1) Yes ____
   (2) No ____
   (3) Not examined ____

5. Bronchitis
   (1) Yes ____
   (2) No ____
   (3) Not examined ____

6. Tuberculosis
   (1) Yes ____
   (2) No ____
   (3) Not examined ____

7. Pneumonia
   (1) Yes ____
   (2) No ____
   (3) Not examined ____

8. Heart Conditions
   (1) Yes ____ If yes: type _____
   (2) No ____
   (3) Not examined ____

9. Other conditions not asked for above

_____

_____

_____

# Personal History

ADDENDUM D

Date ___/___/___

Name:_____ ID#_____

1.

| | | From Year | To Year |
|---|---|---|---|
| Last Residence | _____ Address | ____ | ____ |
| | _____ City State Zip Code | | |
| Prior Residence(s) | _____ Address | ____ | ____ |
| | _____ City State Zip Code | | |
| | _____ Address | ____ | ____ |
| | _____ City State Zip Code | | |

If a complete address cannot be obtained, ask for the cross street and any other information which might identify the residence.

2. Cigarette smoking
   (1) Yes ____
   (2) No ____
   (9) Unknown ____

   If yes:

| Amount Smoked | | #Years |
|---|---|---|
| (1) ≤ 1 pack/day | ____ | _____ |
| (2) > 1 pack/day | ____ | _____ |
| (3) Unknown | ____ | |

3. Marijuana smoking
   (1) Yes ____
   (2) No ____
   (9) Unknown ____

   If yes:

| Amount Smoked | | #Years |
|---|---|---|
| (1) ≤ 5 joint/wk | ____ | _____ |
| (2) > 5 joint/wk | ____ | _____ |
| (9) Unknown | ____ | |

4. Asthma
   (1) Yes ____
   (2) No ____
   (9) Unknown ____

   If yes, since what age? _____

5. Type of death
   (1) Accident ____
   (2) Homicide ____
   (9) Unknown ____

   If homicide:
   (1) Gang related ____
   (2) Innocent bystander ____
   (3) Lover altercation ____
   (4) Family altercation ____
   (5) Other (indicate) ____ _____
   (9) Unknown ____

6. Occupation _____

7. Hobbies _____

8. Other Comments _____

## Autopsy Information

1. ID# _____

2. Date of Death ___/___/___

3. Date of Autopsy ___/___/___

4. Needle Tracks
   (1) Yes ___
   (2) No ___
   (3) Not examined ___

5. Alterations indicative of smoking
   (1) Yes ___
   (2) No ___
   (3) Not examined ___

6. Bronchitis and emphysema
   (1) Yes ___
   (2) No ___
   (3) Not examined ___

7. Tuberculosis
   (1) Yes ___
   (2) No ___
   (3) Not examined ___

8. Pneumonia
   (1) Yes ___
   (2) No ___
   (3) Not examined ___

9. Heart Conditions
   (1) Yes ___ If yes: type _____
   (2) No ___
   (3) Not examined ___

10. Other conditions not asked for above

_____

_____

_____

APPENDIX E

MEETINGS, PHONE CONFERENCES: October - December, 1988

1. **December 5, 1988**, USC School of Medicine

Participants: Dr. Russell P. Sherwin, Ms. Laurie Windle, and Mr. Faisal Bayoumi.

The meeting was held to finalize the data retrieving process at the Coroner's Office and also the procedure for next-of-kin interviews. The discussion centered on the needs for data analysis, especially with respect to defining a standardized list of diagnoses (including key gross and microscopic descriptions of the lungs examined) that could be coded. Ms. Windle was provided with xerox copies of the gross and microscopic descriptions prepared at the time the lungs were examined.

A number of telephone conferences were held with Ms. Laurie Windle, Mr. Steven Dowell (Coroner's Office), and Dr. Nagi Sous (Coroner's Office), and also brief meetings with Mr. Dowell and Dr. Sous at the Coroner's Office to discuss procedures for interviewing the next-of-kin. To permit Ms. Windle to conduct the interviews, Mr. Dowell suggested that Ms. Windle be appointed to the position of Deputy Coroner. Dr. Kornblum subsequently approved an official appointment for her as a volunteer (unsalaried) worker to carry out the interviews. Mr. Dowell agreed to provide her with the case listings, i.e. investigative data pertaining to the lungs acquisitioned for the study.

# PILOT SURVEY OF HUMAN LUNG TISSUE FOR AIR POLLUTION EFFECTS IN LOS ANGELES COUNTY

## QUESTIONNAIRE

The interviewer will read to the participant the text which is underscored as it is written. Text which is not underscored is to instruct the interviewer in the coding and administration of the questionnaire.

PREAMBLE TO THE QUESTIONNAIRE (TO BE ADMINISTERED BY THE INTERVIEWER)

Hello, my name is Dr. Naqi Sous from the Coroner's Office. We just need a little more information on _____; it has to do with where he/she lived and worked, and also a few questions on health. Would you be able to answer just a few questions?

If the respondent says no, then ask:

Is there someone else who could answer these questions?

Obtain the name and telephone number of the other person and ask when would be a good time to reach that person.

If the respondent says yes, then continue with:

Thanks very much for your help. It will take just a few minutes. The reason for calling you is that the Coroner's Office needs information on how the air we breathe at home and at work may be affecting our health. The Coroner is working on this SMOG problem with UCLA and USC, the University of California at Los Angeles and the University of Southern California, and all the information you give us will be confidential. Our reports will not mention any names. We very much need your help, but we want you to know that you don't have to answer our questions if you do not wish to do so.

Name: _____ ID# _____

The interviewer should make clear that by residence we intend to find physical residence and not mailing address. The interviewer should be familiar with the Coroner's Case Report (Form 1) prior to beginning the interview, so that he will be able to verify the most recent address already collected by the coroner's office.

The first thing I'd like to ask is where did _____ live?. I know that _____ lived at: _____

Here the interviewer should state the address from Form 1 and then add:

How long did _____ live there?

For each address, if a complete address cannot be obtained, ask for the cross street and any other information which might identify the residence.

| | | From age | To age |
|---|---|---|---|
| Most Recent Address | _____ Address | _____ | _____ |
| | _____ City State Zip Code | | |

If the age in the "to age" category was less than the age at death, then ask:

Where did _____ live before that and how long did _____ live there?

| | | From age | To age |
|---|---|---|---|
| Prior Residence | _____ Address | _____ | _____ |
| | _____ City State Zip Code | | |

Continue asking prior residences until the residence at birth is reached, by asking again:

Where did _____ live before that and for how long?

| | | From age | To age |
|---|---|---|---|
| Prior Residence | _____ Address | _____ | _____ |
| | _____ City State Zip Code | | |
| | | From age | To age |
| Prior Residence | _____ Address | _____ | _____ |
| | _____ City State Zip Code | | |
| | | From age | To age |
| Prior Residence | _____ Address | _____ | _____ |
| | _____ City State Zip Code | | |

Has _____ always lived there or has _____ ever been away for three months or longer? If so, what was that address and how many months did _____ live at that address?

| | | Number of months |
|---|---|---|
| Most Recent Temporary Address | _____ Address | _____ |
| | | Age |
| | _____ City State Zip Code | _____ |

Did _____ live anywhere else for 3 months or longer? If so, how long did _____ live there?

Number of months

Previous Temporary Address

_____ Address _____

_____ Age

_____ City State Zip Code _____

Now, I would like to ask you whether _____ has ever been sick. Did _____ have any sickness that required a doctor's care, like asthma, for example?

(1) Yes
(2) No
(9) Unknown

If yes, ask:

What did the doctor say it was?

Indicate the diagnosis: _____.

Did smoking bother _____?

Wait for the respondent to answer. If the respondent does not state whether the deceased was a smoker, then ask:

Do you have any idea if _____ smoked?

(1) Yes
(2) No
(9) Unknown

If yes, ask: What did _____ smoke?

(1) Cigarettes
(2) Marijuana

If yes to cigarettes, ask:

How many cigarettes did _____ smoke? How long did _____ smoke?

Please indicate amount below according to what respondent indicates.

| Amount Smoked | # Years |
|---|---|
| (1) <= 1 pack/day | _____ |
| (2) > 1 pack/day | _____ |
| (3) Unknown | _____ |

If the respondent does not seem to be sure about the amount smoked, ask whether _____ smoked less than one pack per day or more than one pack per day.

If yes to marijuana, ask:
About how much marijuana did _____ smoke? How long did _____ smoke?

| Amount Smoked | # Years |
|---|---|
| (1) <= 5 joints/week | _____ |
| (2) > 5 joints/week | _____ |
| (3) Unknown | _____ |

Did _____ work?

(1) Yes
(2) No
(3) Unknown

Would you tell me where _____ worked?

Indicate where: _____.

How long did _____ work there?

Indicate the number of months worked. _____.

Do you know whether _____ was exposed to any dust or fumes at work?

(1) Yes
(2) No
(3) Unknown

If yes, to what type of dust or fumes was _____ exposed?

Indicate substance to which s/he was exposed. _____.

In addition to _____'s regular job, did he/she have a second job or do his/her own work for pay, or for fun?

(1) Yes
(2) No
(3) Unknown

If so, indicate what he/she did, and for how long.

How long did _____ do this?

| Other job, activity, or hobby: | How long. From age to age: |
|---|---|
| (1) _____ | _____ |
| (2) _____ | _____ |
| (3) _____ | _____ |
| (4) _____ | _____ |

At the end of the interview, say:

Thank you for answering these questions about _____ for us. Your cooperation will be of great help to the doctors and scientists working to bring everyone better health through cleaner air. We very much appreciate your taking the time to answer our questions.

The interviewer should find out who is answering the questionnaire and what the relationship is with the deceased by asking:

Would you mind telling me your name in case I need to check some item with you?

Name of respondent: _____.

What is your relationship to _____?

Indicate relationship: _____.

Again, many thanks for your help. Goodbye!

Additional information to be completed by investigator but not asked as part of the interview

Type of death
(1) Accident _____
(2) Homicide _____ If homicide, indicate additional information:

(1) Gang related _____
(2) Innocent bystander _____
(3) Lover altercation _____
(4) Family altercation _____
(5) Other (indicate) _____
(9) Unknown _____

(3) Unknown _____

APPENDIX F

MEETINGS, PHONE CONFERENCES: January - April, 1989

1. February 10, 1989, UCLA.

Participants: Virginia Clark, Roger Detels, Steve Dowell, John Moore, Valda Richters, Russell P. Sherwin, Dane Westerdahl, and Laurie Windle.

The agenda of the meeting is summarized in the attached Dr. Detels letter of February 14, 1989. In addition, Ms. Windle met with Mr. Corey Kagan of the L.A. County Coroner's Office to arrange the retrieval of information needed for contacting the next-of-kin, in particular the pertinent telephone number and address.

A number of telephone conferences and meeting were held with Ms. Laurie Windel, Mr. Steven Dowell (Coroner's Office), and Mr. Corey Kagan (assistant to Mr. Dowell) to discuss improvements in data aquisition, in particular with respect to letter introductions, telephone conversations, and personal interviews. A plan was developed to improve the cooperation of the next-of-kin through a more immediate contact by letter. The jointly constructed letter was approved by the UCLA Human Subject Protection Committee on April 19, 1989 (see enclosure), Mr. Steven Dowell, and by Dr. Ronald Kornblum.

In addition, Dr. Sherwin met with Mr. Dowell on a number of occasions following the routine checking of the daily case listings at the Coroner's Office each morning. One meeting included a search of the case records to find a means of expediting the contacting of next-of-kin. We learned that there were two sources of information that have not been utilized, records of the Property Section of the Coroner's Office, and also records in the Coroner's Office containing mortuary data, in particular next-of-kin telephone numbers and addresses. The latter two sources will be searched by Mr. Kagan as part of his routine participation in the project. Dr. Sherwin has also been in frequent telephone contact with Ms. Windle to facilitate the interviews. A tabulation of progress made in the interviews was submitted to Dr. Sherwin (see enclosure). A revised questionaire was prepared by Dr. Detels for use by Ms. Windle (see enclosure), and arrangements for foreign language assistance with the interviews are being made by Dr. Detels.

Russ handed out a summary of the types of lesions he would be coding from the autopsies. The diagnostic categories for outcome would be:

- bronchitis, chronic inflammation
- bronchiolitis, chronic inflammation
- desquamative peribronchiolar pneumonitis
- chronic interstitial pneumonia
- emphysema, centrilobular and/or panlobular

Valda will transfer an additional $2,000-3,000 into the UCLA subcontract so we can continue to pay Laurie.

Please let me know if I have committed any errors of omission or commission.

Thanks.

Sincerely,

Roger Detels (RR)

Roger Detels, M.D., M.S.
Professor

cc: Mary Jane Varley

(Dictated but not read.)

UNIVERSITY OF CALIFORNIA, LOS ANGELES

UCLA

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SANTA BARBARA · SANTA CRUZ

SCHOOL OF PUBLIC HEALTH
10833 LE CONTE AVENUE
LOS ANGELES, CALIFORNIA 90024-1772

February 14, 1989

received
2/22/89

To: Russ Sherwin
Valda Richter
Dane Westerdahl
John Moore
Steve Dowell
Virginia Clark
Laurie Windle

This memo will, hopefully, summarize our meeting of February 10. Thank you all for coming.

In terms of interviewing, our biggest problem to date has been getting a correct telephone number for the next of kin. Laurie will provide Steve with the names of the cases for which she has been unable to obtain a telephone number so that he can check back with the individual investigator to see if he can get a recent telephone number. In addition, Russ will tell Steve which cases have been selected in the future so that the investigators will know that we need a telephone number for the next of kin.

We have been getting primarily cases of violence and few of the accident cases. Steve will investigate our getting the accident cases as well since they are more likely to be in areas other than the south central area from which most of the violence cases come. We will need geographic distribution if we are to make correlations to a range of pollutant exposures.

John and Dane will provide us with tapes of pollutant exposures for the census tracts that we have identified from the study as places of residence of the cases. We will obtain the number of hours exceeding selected thresholds for $O_3$, $NO_2$, total suspended particulates (TSP) and $SO_4$ for each year from 1973-1987. We will send the list of census tracts when we have completed the next of kin interviews. John and Dane will select those thresholds which they feel will provide the best differentiation of exposure to each pollutant.

Russ will do fluorescent exam of lungs for identification of possible smokers. For those individuals who are positive, but for whom there is a negative smoking history we will consider measuring nicotine levels.

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SCHOOL OF PUBLIC HEALTH
10833 LE CONTE AVENUE
LOS ANGELES, CALIFORNIA 90024-1772

LETTER TO BE SENT TO NEXT-OF-KIN

Dear _____,

Through the Los Angeles County Coroner's office, we have been informed of the sad loss of your _____. We know that you are still suffering from his/her loss, and we recognize the hardship you may be under. Perhaps, you would be willing, however, despite your terrible loss to help us to avoid similar trauma to other families by helping us to answer a few questions. They have to do with determining if changes in _____ lung's may have been related to exposure to air pollution.

We have been concerned that exposure to the types of air pollutants which are common in Southern California may be causing serious respiratory disease in people. Recent studies at UCLA have suggested that changes in the lung due to exposure to air pollution may begin before 25 years of age. Unfortunately, identification of these early changes is difficult to measure using currently available tests of breathing ability. We must, therefore, examine from people under twenty-five years of age to identify these early changes. We are cooperating with the Los Angeles County Coroner's Office to study the lungs of young people living in California who have died, to look for changes in their lungs which may have been due to exposure to air pollution. Autopsies are routinely performed on all fatal accident investigations as a matter of law and are not carried out specifically as part of this study.

One of our research associates can ask you these questions over the telephone in about 15-20 minutes. The questions s/he would ask about _____ may include the following:

respiratory conditions or diseases
personal habits (e.g.: smoking, drinking)
occupations and hobbies
places of schooling
places where _____ lived

We know that this is a difficult time for you, but your answers to these questions can help us to learn more about how air pollution causes respiratory disease and may ultimately help in preventing future residents of Southern California from suffering respiratory disease because of exposure to air pollution. You are under no obligation to participate in this study, and if you decide to participate, you may decline to answer any question. All information collected will be confidential. You will be called by telephone in approximately one week. At that time you may decide to participate or not. If you prefer, you can contact us at (213) 206-3379 or write to us at the addresses below to indicate whether or not you wish to be called. If you have any questions about the study, please call us collect at (213) 206-3379 between 9 A.M. and 5 P.M.

Since we do not know your telephone number, could you call (213) 206-3379 and let us know if you would be willing to be interviewed. If you are willing, we can probably interview you at that time. You may also let us know that you do not wish to be interviewed or further contacted.

Sincerely,

Russell Sherwin, MD
Professor of Pathology
USC School of Medicine
Department of Pathology, HMR-201
2011 Zonal Avenue
Los Angeles, CA 90033

Roger Detels, MD MS
Professor of Epidemiology
School of Public Health
University of California,
Los Angeles
Los Angeles, CA 90024

ORIGINAL
REVISED

# PILOT SURVEY OF HUMAN LUNG TISSUE FOR AIR POLLUTION EFFECTS IN LOS ANGELES COUNTY

## QUESTIONNAIRE

The interviewer will read to the participant the text which is underscored as it is written. Text which is not underscored is to instruct the interviewer in the coding and administration of the questionnaire.

PREAMBLE TO THE QUESTIONNAIRE (TO BE ADMINISTERED BY THE INTERVIEWER)

Hello, my name is _____ from the Coroner's Office. We just need a little more information on _____ ; it has to do with where he/she lived and worked, and also a few questions on health. Would you be able to answer just a few questions?

If the respondent says no, then ask:

Is there someone else who could answer these questions?

Obtain the name and telephone number of the other person and ask when would be a good time to reach that person.

If the respondent says yes, then continue with:

Thanks very much for your help. It will take just a few minutes. The reason for calling you is that the Coroner's Office needs information on how the air we breathe at home and at work may be affecting our health. The Coroner is working on this SMOG problem with UCLA and USC, the University of California at Los Angeles and the University of Southern California, and all the information you give us will be confidential. Our reports will not mention any names. We very much need your help, but we want you to know that you don't have to answer our questions if you do not wish to do so.

Name: _____ ID# _____

The interviewer should make clear that by residence we intend to find physical residence and not mailing address. The interviewer should be familiar with the Coroner's Case Report (Form 1) prior to beginning the interview, so that s/he will be able to verify the most recent address already collected by the coroner's office.

The first thing I'd like to ask is where did _____ live?. I know that _____ lived at: _____

Here the interviewer should state the address from Form 1 and then add:

How long did _____ live there?

For each address, if a complete address cannot be obtained, ask for the cross street and any other information which might identify the residence.

| | | From (year) | To (year) |
|---|---|---|---|
| Most Recent Address | _____ Address | _____ | _____ |
| | _____ City State Zip Code | | |

If the age in the "to age" category was less than the age at death, then ask:

Where did _____ live before that and how long did _____ live there?

| | | From (year) | To (year) |
|---|---|---|---|
| Prior Residence | _____ Address | _____ | _____ |
| | _____ City State Zip Code | | |

Continue asking prior residences until the residence at birth is reached, by asking again:

Where did _____ live before that and for how long?

| | | From (year) | To (year) |
|---|---|---|---|
| Prior Residence | _____ Address | _____ | _____ |
| | _____ City State Zip Code | | |
| | | From (year) | To (year) |
| Prior Residence | _____ Address | _____ | _____ |
| | _____ City State Zip Code | | |
| | | From (year) | To (year) |
| Prior Residence | _____ Address | _____ | _____ |
| | _____ City State Zip Code | | |

Has _____ always lived there or has _____ ever been away for three months or longer? If so, what was that address and how many months did _____ live at that address?

| | | From (year) | To (year) |
|---|---|---|---|
| Most Recent Temporary Address | _____ Address | _____ | _____ |
| | _____ City State Zip Code | _____ | _____ |

Did _____ live anywhere else for 3 months or longer? If so, how long did _____ live there?

| | | From (year) | To (year) |
|---|---|---|---|
| Previous Temporary Address | _____ Address | _____ | _____ |
| | _____ City State Zip Code | _____ | _____ |

Now, I would like to ask you whether _____ has ever been sick. Did _____ have any sickness that required a doctor's care, like asthma, for example?

(1) Yes
(2) No
(9) Unknown

If yes, ask:

What did the doctor say it was?

Indicate the diagnosis: _____.

Did smoking bother _____?

Wait for the respondent to answer. If the respondent does not state whether the deceased was a smoker, then ask:

Do you have any idea if _____ smoked?

(1) Yes
(2) No
(9) Unknown

If yes, ask: What did _____ smoke?

(1) Cigarettes
(2) Marijuana

If yes to cigarettes, ask:

How many cigarettes did _____ smoke? How long did _____ smoke?

Please indicate amount below according to what respondent indicates.

| Amount Smoked | # Years |
|---|---|
| (1) <= 1 pack/day | _____ |
| (2) > 1 pack/day | _____ |
| (3) Unknown | _____ |

If the respondent does not seem to be sure about the amount smoked, ask whether _____ smoked less than one pack per day or more than one pack per day.

If yes to marijuana, ask:

About how much marijuana did _____ smoke? How long did _____ smoke?

| Amount Smoked | # Years |
|---|---|
| (1) <= 5 joints/week | _____ |
| (2) > 5 joints/week | _____ |
| (3) Unknown | _____ |

Did _____ work?

(1) Yes
(2) No
(3) Unknown

Would you tell me where _____ worked?

Indicate where: _____.

How long did _____ work there?

| | From (year) | To (year) |
|---|---|---|
| | _____ | _____ |

Do you know whether _____ was exposed to any dust or fumes at work?

(1) Yes
(2) No
(3) Unknown

If yes, to what type of dust or fumes was _____ exposed?

Indicate substance to which s/he was exposed. _____.

Did _____ work anywhere prior to this?

(1) Yes
(2) No
(3) Unknown

If yes, continue asking prior positions until the first job is reached.

If no, continue in the next section with "In addition to _____'s regular job..."

Would you tell me where _____ worked?

Indicate where: _____.

How long did _____ work there?

| | From (year) | To (year) |
|---|---|---|
| | _____ | _____ |

Do you know whether _____ was exposed to any dust or fumes at work?

(1) Yes
(2) No
(3) Unknown

If yes, to what type of dust or fumes was _____ exposed?

Indicate substance to which s/he was exposed. _____.

Did _____ work anywhere prior to this?

If yes, continue asking prior positions until the first job is reached.
If no, continue in the next section with "In addition to _____'s regular job..."

Would you tell me where _____ worked?

Indicate where: _____.

How long did _____ work there?

| | From (year) | To (year) |
|---|---|---|
| | _____ | _____ |

Do you know whether _____ was exposed to any dust or fumes at work?

(1) Yes
(2) No
(3) Unknown

If yes, to what type of dust or fumes was _____ exposed?

Indicate substance to which s/he was exposed. _____.

Did _____ work anywhere prior to this?

If yes, continue asking prior positions until the first job is reached.

If no, continue in the next section with "In addition to _____'s regular job..."

Would you tell me where _____ worked?

Indicate where: _____.

Additional information to be completed by investigator but not asked as part of the interview

Type of death
(1) Accident _____
(2) Homicide _____ If homicide, indicate additional information:

(1) Gang related _____
(2) Innocent bystander _____
(3) Lover altercation _____
(4) Family altercation _____
(5) Other (indicate) _____
(9) Unknown _____

(3) Unknown _____

PH 596
Dr. Detels
March 27, 1989

# Pilot Survey of Human Lung Tissue for Air Pollution Effects in Los Angeles County
## Report and Recommendations

Laurie L. Windle

Introduction

The effects on human lung tissue to long-term exposure to air pollution have been characterized in various studies. However, the need to document early changes presents a unique challenge. The rationale for this pilot study of the effects on human lung tissue was to document early lung function changes related to exposure to air pollutants. A case was defined as a coroner's case between the ages of 15 and 25 years of age who died of accidental causes, homicide or suicide without pre-existing illness. The motivation for this study was to look at exposures in a young, relatively healthy population. This was to be accomplished by removal of the lungs and subsequent pathological analysis to determine the extent and/or severity of any abnormalities in the lung tissue. A questionnaire was developed to assess whether any of the pathology findings could be attributed to variables other than air pollution exposure. The questionnaire was administered to the next-of-kin of cases to identify and characterize place and duration of residence, smoking history, health status, occupation and whether occupation involved exposure to any dust or fumes that might contribute to any changes in lung function. The study involved the joint cooperation between the University of Southern California (U.S.C.), the University of California, Los Angeles (U.C.L.A.) and the Los Angeles County Coroner's Office.

The function of the Coroner's Office was to alert the pathologist at U.S.C., Dr. Sherwin, about incoming coroner's cases who met the case definition of the study. Selecting coroner's cases allowed the study to access the lung tissue that belonged to the coroner for which the study is required to provide any data obtained to the Coroner's office.

The University of Southern California provided the pathological examination and analysis of the lung tissue, and characterization of the extent and/or severity of any abnormal findings or disease. The pathology findings are done by Dr. Sherwin who was responsible for defining the nature

of disease and characterization of pathological findings.

The University of California, Los Angeles coordinated various aspects of the study between UCLA, USC, and the Coroner's Office. Additionally, the Staff Research Associate is responsible for obtaining environmental exposure information from the Air Resources Board (ARB), the exchange of information between the Coroner's Office and UCLA regarding the cases and current information on the cases; for example, next-of-kin phone numbers, as well as to develop and administer the questionnaire about health status, occupation and residence information over the telephone to the next-of-kin.

The role of the questionnaire is extremely important in identifying any variables which may impact upon lung function changes. Therefore, the purpose of this report is summarize the results of the interviews to date. Additionally, the focus of this report will be to make recommendations concerning the future role of the interviews in this study.

The following is a preliminary summary of the pilot study interviews.

There were a total of twenty nine initial cases received from the Coroner's Office for which interviews were attempted.
Seventeen of 29 or 59% were unable to be contacted for the following reasons:

| | UNABLE TO CONTACT | | 17/29 = 59% |
|---|---|---|---|
| Reason: | Number | % subtotal | % overall |
| Phone number was missing from the Coroner's Office | 5 | 5/17 = 29 | 5/29 = 17 |
| Wrong number listed on the report from Coroner's Office | 5 | 29 | 17 |
| Report indicated there was no phone | 4 | 24 | 14 |
| Phone number listed was disconnected without any forwarding information | 3 | 18 | 10 |
| Total | 17 | 100 | 59 |

Among those contacted, excluding the one disqualified subject who did not meet the case definition, approximately 60% were successfully interviewed and 40% refused.

CONTACTED 11/29 = 38%

| Disposition: | Number | % subtotal | % overall |
|---|---|---|---|
| Interview completed | 6 | 54 | 21 |
| Refused | 4 | 36 | 14 |
| Disqualified (Subject had pre-existing illness/too old) | 1 | 9 | 3 |
| Total | 11 | 100 | 38 |

DISQUALIFIED WITHOUT ATTEMPT TO CONTACT

| Reason: | Number | % subtotal | % overall |
|---|---|---|---|
| Disqualified (subject was too young) | 1 | 100 | 3 |
| Total | 1 | 100 | 3 |
| | 29 | - | 100 |

Overall, six interviews were completed from the initial 29 cases received; this represents a net yield of 21%. Excluding the two disqualified interviews which did not meet the case definition of the study because one was too young and the other was too old as well as dying from natural causes, the completed interviews from initial cases would be 22%. There are two major areas to address based upon the information to date; that is: among those who were unable to be contacted and among those who were able to be contacted. By far, the greatest concern in this study, to date, is addressing reasons for failure to contact a majority of cases.

Among those cases unable to be contacted, 59% of total cases (17/29) had insufficient and/or erroneous information that prevented contacting next-of-kin. The greatest difficulty among these cases was obtaining a correct phone number from the Coroner's Office records. When an additional attempt was made to verify the accuracy of this information the result was nil; that is, this lack of information from the first set of records obtained that led to a second request of verification of information on 14/17 cases did not yield any new information. We were only able to receive any verification on 3/14 requests. One of the three second requests received was a duplicate of information already received while 2/3 were incorrect case numbers; that is, they did not correspond to those case numbers requested. The remaining 11/14 requests supposedly were files that could no longer be found. In a memorandum accompanying the result of the request for verification of information, it was stated that people often do not have telephones or give false information. The additional problem of flow of information and correct case number identification still needs to be addressed. This initial effort represents an enormous amount of unavailable data if further efforts to locate next-of-kin are not secured.

Among those contacted, excluding the disqualified subject, the data reveal that, 40% refused and 60% were successfully completed interviews. Excluding, the 59% who were unable to be contacted as well the 14% who refused overall, the net yield of completed interviews is less than a quarter of total cases.

## RECOMMENDATIONS & SUGGESTIONS

Prior to making any recommendations, I would like to qualify any suggestions by emphasizing the small sample size that has been dealt with so far. Based upon the preliminary interviews, suggestions could be best be made in three areas: first, obtaining more accurate and timely procurement of contact information for the next-of-kin from the Coroner's Office; secondly,

the possible creation of a preliminary letter sent to the next-of-kin prior to phone contact to indicate that an interviewer will be calling from the study; and finally, failing adoption of a better system to expedite and ameliorate the exchange of information from the Coroner's Office, consideration of alternatives to administration of the questionnaire with possible greater emphasis on the pathology findings.

Regarding acquisition of contact information for the next-of-kin from the Coroner's Office, it would seem that alternatives to the current method of obtaining telephone numbers from the Coroner's Case Report Form should be investigated. Namely, both the mortuary and the Property Department at the Coroner's Office have this information on next-of-kin. Specifically, the mortuary would seem to be a better source of information, assuming they have a billing address and, hopefully, a correct phone number. A meeting has been set for Tuesday, March 28, 1989 to discuss these alternatives between myself and Corey Kagan, a representative of the Coroner's Office, assigned to assist Steve Dowell in collecting information for this study. The result of these alternative methods of obtaining telephone numbers will be addressed as well as discussing a time frame for completion of the information since time is a critical issue at this point. Any additional changes that need to be made to expedite the process will also be discussed in an attempt to facilitate the exchange of information in a more timely and accurate manner. Failing positive results from this meeting, one suggestion might be that I be considered as a candidate to do record searches at the Coroner's Office. In this instance, the loss or delay of information through clerical errors would, hopefully, be resolved.

The second suggestion of writing a letter to the next-of-kin prior to the telephone call is based upon this interviewer's, admittedly anecdotal, impression that the next-of-kin seem to be very confused about the nature of

the telephone inquiry and whether it is, in fact, still part of the Coroner's investigation. This is particularly a problem the more time that has elapsed since death of the case. Ideally, the letter would briefly acquaint the next-of-kin with the nature of the telephone inquiry while emphasizing the very brief nature of the interview which would be limited to five to ten minutes.

The final suggestion is consideration of alternatives to administration of the questionnaire to next-of-kin in favor of a greater emphasis on the pathology findings in the event that better contact information cannot be assured. Reliance on the pathology findings to address issues that would normally be obtained by the questionnaire would require that the assays used by the pathologist be extremely sensitive to detecting smoking history. To date, it appears this issue of sensitivity of the cotinine assay remains questionable. Further, without the interview, the collection of place and duration of residence history would be problematic. Taking into the consideration the young age of cases in this study, record searches through the usual vital statistics records would be both time consuming and of questionable reliability.

Based upon the limited number of initial cases and the delay in the early cases between time of death and attempt to contact the family, as well as the difficulties in establishing an alternative, such as the vital record search mentioned above and its inherent problems of reliability, the recommendation of this interviewer would be to continue the interviews at least until the end of the pilot phase. This would allow for the determination of whether the non-response pattern would remain steady with greater numbers. Additionally, this would allow time to evaluate changes to be initiated to ameliorate the exchange of information between the Coroner's Office and U.C.L.A. already suggested in this report. Ultimately, I believe it would be best to re-evaluate the nature of the study at the end of the pilot phase. The critical nature of the place and duration of residence

variable and smoking status are very important. The important consideration here would seem to be toward obtaining accurate information about this particular population which would ideally be best obtained from the next-of-kin. For these reasons, I would stress the preference to continue efforts to improve the quality and timely acquisition of contact information from the Coroner's Office, or alternatively, the mortuary or Property department of the Coroner's Office.

APPENDIX H

PUBLICATIONS

Submitted to Journal of Air Waste and
Management Association

# CENTRIACINAR REGION (CAR) DISEASE IN THE LUNGS OF YOUNG ADULTS
## A PRELIMINARY REPORT

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Supported in part by California Air Resources Board Contract A6-202-33, and by the Hastings Foundation.

## ABSTRACT

The lungs of 107 youths (14-25 years of age), who died in vehicular accidents or were homicide victims, were examined to determine the extent and severity of centriacinar region (CAR) disease. The lungs of 11 youths had been excluded for marked congestion, hemorrhage, or poor preservation. We defined CAR disease as a chronic inflammation of the respiratory bronchiole and its proximal acinic structures, with an accompanying histiocytic desquamation. The more severe forms of CAR disease were identified by an accompanying interstitial, histiocytic infiltration of acinic walls (bronchioles to alveoli), with or without peribronchiolar and interstitial chronic inflammation and fibrosis. Of the 107 youths, 29 had severe CAR disease as judged by scores of 5 or more (on a scale of 1-10) for both severity and extent. There were 51 cases with scores of 1 to 4 (slight to moderate), and 27 with minimal or no evidence of CAR disease in the four sections of lung examined. The pathogenesis is undoubtedly multifactorial and most likely reflects to a large extent a suboptimal socioeconomic status, a high frequency of lung infection, excessive smoking, high levels of air pollution, and other environmental toxicants. Air pollution is highly suspect since the basic lesion, the same relatively mild respiratory bronchiolitis found with smoking and dust exposures (without the pigment deposits), has been produced in primates and other animals by ambient levels of ozone. We did not find evidence for the granulomatous lung disease of hard drug users, and known drug users were excluded. The demographic study, and in particular data on smoking and metabolic products (cotinine and cannabinoid) are pending. The high incidence and severity of CAR disease in youths is unprecedented and cannot be attributed to any single agent. The results strongly suggest not only an impending rise in overt lung disease for corresponding subpopulations now living, but some measure of increase in the rate of lung decline for the population in general.

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# NITROGEN DIOXIDE ($NO_2$) INHALATION, FORMATION OF MICROTHROMBI IN LUNGS AND CANCER METASTASIS

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*It is recognized that cancer cells may be introduced into circulation during surgical removal of a malignant neoplasm. The fate of these cells depends upon many factors. In this paper we present findings from an animal model which indicate that inhalation of nitrogen dioxide facilitates blood-borne cancer cell metastasis to lungs by injuring lung capillary endothelium and formation of microthrombi. Lung capillaries were evaluated by light and electron microscopy. The main lesions observed were microthrombi and injury to capillary endothelial cells, following 6 weeks of 0.35 ± 0.05 ppm $NO_2$ exposure. The blood-borne cancer cell metastasis was studied utilizing B16 melanoma cells in C57Bℓ/6J mice. A correlation was observed between increased incidence of microthrombi, endothelial cell injury and lung metastasis in exposed animals. Other adverse $NO_2$ effects such as impairment of immune system may also participate. Inhalation of nitrogen dioxide and other air pollutants may play a significant role in enhancement of metastasis and blood vessel associated disorders.*

## INTRODUCTION

It is recognized that during surgical procedures designed to remove malignant neoplasms, many malignant cells may be released into circulation and in some instances, these events have been referred to as "showers" of cancer cells (Roberts et al., 1962; Salsbury, 1977; Butler and Gullino, 1975). The biological consequences of such episodes will depend upon the type of cancer, other therapeutic modalities and the condition of the patient. The interaction of blood-borne cancer cells with host determines the final outcome. The dreaded outcome, of course, is the dissemination of cancer cells throughout the body. Fortunately, the body has a very extensive defense network against such events and only few of the blood-borne cancer cells, on the order of 0.01%, manage to escape this defense network. However, if the defense network is impaired, more cancer cells will survive and it will be more difficult to eradicate the increased number of cells by other means. In view of this, the question arises as to what conditions could influence the survival of blood-borne cancer cells. In general, it has been accepted that injury to vascular lining cells, suppression of certain cells in the immune system and

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2. Abbreviations: SHA-C: Simulated high altitude (380 mm Hg); no ozone exposure; SHA-X: Simultated high altitude; 0.35 ppm ozone exposure; SL-C: No simulated high altitude; no ozone exposure; SL-X: No simulated high altitude; 0.35 ppm ozone exposure.

3. Key words: elastin; high-altitude; image analysis; lung; ozone.

# THE EFFECT OF OZONE AND SIMULATED HIGH ALTITUDE ON MURINE LUNG ELASTIN: QUANTITATION BY IMAGE ANALYSIS

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*Four subgroups of a colony of 50 mice were housed in environmental chambers supplied by particle- and pollutant-filtered air. The animals were exposed to 0.35 ppm ozone and/or simulated high altitude (380 mm Hg) for four weeks, with exposure 4 1/2 hours/day and 5 days/week. Lung elastin area and alveolar wall area were quantitated by computer assisted image analysis of paraffin embedded sections stained with aldehyde fuchsin and metanil yellow. Compared to the controls, the combination of ozone and simulated high altitude resulted in a 54.5% increase in lung elastin area ($p < 0.005$), and simulated high altitude by itself increased elastin area by 19.6% ($p < 0.05$). Simulated high altitude with and without ozone exposure also increased alveolar wall area (24.8%, $p < 0.01$; and 9.7%, NS, respectively). Ozone exposure alone had a reverse effect: a 16.1% decrease in elastin area ($p < 0.1$), and a 6.5% decrease in alveolar wall area (NS). Since an intact lung scaffolding is required for full restoration of injured alveolar epithelium and since intact lung elastin is critical for proper lung compliance, the results suggest that ozone exposure at high altitude is most likely to have an adverse effect on lung structure and function.*

# INFLUENCE OF AMBIENT LEVEL $NO_2$ EXPOSURE ON NEWBORN AND ADULT MICE BODY WEIGHTS

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*A study of the effects of $NO_2$ inhalation on body weights of newborn and adult mice was carried out. A total of 1590 adult mice and 450 newborn mice were evaluated. The level of $NO_2$ exposure was in the ambient range and varied between 0.17 and 0.80 ± 0.05 ppm depending on experimental design. The duration of exposure was three to twelve weeks, depending upon specific experimental design. The results have indicated that newborn mice are more sensitive than adults to the inhalation of ambient level $NO_2$ and showed significantly lower body weight gains. The findings were interpreted as being indicative of adverse systemic $NO_2$ effects on newborn animals.*

## INTRODUCTION

There are many reports of altered lung structure and function following nitrogen dioxide ($NO_2$) exposure (Coffin and Stokinger, 1977; Dawson and Schenker, 1979; Guidotti, 1978; Nakajima *et al.*, 1980) and several studies have indicated extra pulmonary effects as well (Mersch *et al.*, 1973; Sherwin) and Layfield, 1974; Maigetter *et al.*, 1978; Holt *et al.*, 1979; Oda *et al.*, 1980; Miller *et al.*, 1980). Thus, there are strong indications that $NO_2$ inhaltion can exert systemic effects and this is not surprising since it has been shown that $NO_2$ or its reaction products may be distributed systemically (Goldstein *et al.*, 1977; Yoshida *et al.*, 1980; Parks *et al.*, 1981). Moreover, adverse effects of $NO_2$ at a systemic level could be expected to influence the overall growth process, which could be reflected in the body weights of exposed animals. A simple evaluation of body weights following $NO_2$ exposure, especially in young developing animals, should reveal a positive or negative correlation with $NO_2$ inhalation exposure. To date, we are aware of only three reports focusing specifically on body weights following *ambient* level $NO_2$ exposures (Csallany and Ayaz, 1978; Kuraitis *et al.*, 1981; Haydon *et al.*, 1965). Of particular interest are the two studies which reported lower body weights in the $NO_2$ exposed animals. One of these studies (Csallany and Ayaz, 1980) combined body weight data from animals exposed to 0.50 and 1.0 ppm $NO_2$ and

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# THE INFLUENCE OF COMMUNITY AIR POLLUTION ON THE LUNGS OF MICE.
## Part II: Image Analysis Quantitation of Lung Elastin

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ABSTRACT

Four groups of male Swiss-Webster mice were equally divided, with two exposed continuously to outdoor air in Central Los Angeles (LA) and Santa Barbara (SB), and two indoors, Room Air (RA) and pollutant filtered room air (C). Nearby monitoring stations provided data on nitrogen dioxide ($NO_2$), ozone ($O_3$), sulfur dioxide, carbon monoxide, hydrocarbons, and particulates. The left lungs of all mice were perfusion-inflated with 10% buffered formalin at 25 cm water pressure and lung sections were stained with aldehyde fuchsin for elastic fibers. The monitoring data showed 21 exceedences of the State $O_3$ standard for Los Angeles over the 43 day test period, but only two for Santa Barbara at just above the Standard level. The mean value for the one hour average $O_3$ level in LA during the 43 days was 0.11ppm, vs 0.03ppm for Santa Barbara. Mean $NO_2$ levels in LA were four times higher, 0.12ppm vs 0.03ppm for Santa Barbara. The levels recorded for other pollutants (carbon monoxide, $NO_2$, sulfur dioxide, particulates, and hydrocarbons) were also consistently greater for LA. $O_3$ levels were partly scrubbed by the partial enclosures of housings for the outdoor LA and SB animals, but $O_3$ levels for the LA animals still exceeded the $O_3$ Standard 5 times, vs 21 for the monitoring station. $O_3$ was not detected for the C group, and the RA animals had values lower than those for LA. The LA animals had the largest amount of elastin according to total area per field and the SB group the least (LA vs SB; $p=.03$). The Mean Elastic Fiber Area was also highest for the LA animals and lowest for the animals housed in Santa Barbara, but with the difference at a borderline level of statistical significance ($p<.09$), and this was also true for Mean Elastic Fiber Linear Intercepts and Perimeters ($p<.07$ and $p<.06$ respectively). Elastic Fiber Numbers did not differ significantly. There were no significant differences in alveolar wall area wth one exception at a borderline level of significance (C>RA, $p<.08$). Lung volumes varied from a low of 141.9ul (LA) to a high of 149.5 ul(RA), with intergroup but not intragroup differences, i.e. indoor vs outdoor groups. The increase in elastin is in accord with the majority of experimental animal studies of elastin responses to injury, including amiodarone and cadmium chloride induced fibrosis, and the elastase and papain models of emphysema. A faulty elastogenesis seems to be involved. Differences between alveolar wall thickening in frozen section preparations and paraffin sections are believed to represent in part the loss of proteinaceous edema fluid with paraffin processing. The findings suggest an altered lung elasticity and a suboptimal scaffolding that hinders complete regeneration of the overlying epithelium.

# ACUTE AND CHRONIC PERICHOLANGIOLITIS IN ASSOCIATION WITH MULTIFOCAL HEPATIC LYMPHANGIOMATOSIS

LAKSHMANAN SATHYAVAGISWARAN, MD, AND RUSSELL P. SHERWIN, MD

*Multifocal, lymphangiomatous lesions were found in the right lobe of the liver of a 9-year-old girl who died seven days after head trauma. We believe the lesions represent a cystic and pseudoneoplastic dilatation of liver lymphatics secondary to a posttraumatic complication, acute and chronic inflammation primarily of small bile ducts, and canaliculi (pericholangiolitis). The findings provide new evidence that inflammation and fluid overload, in the absence of a congenital malformation, are cardinal factors in the pathogenesis of some forms of lymphangiomatosis.* HUM PATHOL *20:601–603.* © *1989 by W.B. Saunders Company.*

## REPORT OF A CASE

A 9-year-old female was thrown off her bicycle while racing down hill. Her head struck the curb of the sidewalk and she was rendered unconscious. Following admission to the local hospital, multiple fractures were found involving the left parietal, temporal, frontal, and occipital bones, with herniation of the frontal and other lobes of the brain through the fracture sites. In addition, the left middle meningeal artery was lacerated. An emergency craniotomy was performed with removal of a large portion of the left frontal lobe and portion of parietal lobe, and a patch of dura placed over the exposed brain. Two days after surgery, she became unresponsive to all stimuli, and an EEG showed a flat line. A right upper lobe infiltrate was treated with antibiotics. With the family in complete agreement with the conclusion of the physicians that she had in effect died a cerebral death, the respirator was discontinued and she was pronounced dead seven days after admission.

At autopsy, the craniocerebral injuries were the major findings. The only other site of abnormality was in the liver. The liver weighed 1,400 g and its cut surface demonstrated multiple, yellowish-white circumscribed areas 2 mm to 3 mm in diameter, and predominantly in the right lobe (Fig 1, top). On microscopic examination, the cystic spaces were empty or contained a pale eosinophilic material. The cystic spaces were distributed in a radial fashion within the midzones of liver lobules (Fig 1, bottom) and were continuous with perivascular and periductal lymphatic spaces of the triad (Fig 2, top left). An unexpected finding was the presence of a widespread acute and partly chronic inflammation of the biliary tree that mainly involved small ducts and canaliculi. The inflammation was multifocal and most prominent in areas of cystic dilatation. There were occa-

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# Desquamative Interstitial Pneumonia in an Infant

## Mimicry of Sudden Infant Death Syndrome

Irwin L. Golden, M.D., and Russell P. Sherwin, M.D.

A 15-week-old infant girl, without a prior history of overt illness, was found dead while sleeping between her two parents. The gross examination at autopsy showed only congested lungs, and the initial diagnosis was sudden infant death (SID). On microscopic examination, a desquamative interstitial pneumonia (DIP) was observed. The widespread, patchy intraalveolar histiocytic desquamation was associated with lymphocytic infiltration of bronchiolar and aveolar walls, which together provided convincing evidence that an interstitial pneumonitis was the cause of death. A viral etiology seems most likely in view of the accompanying chronic inflammation of bronchial submucosal glands.
**Key Words:** Desquamative interstitial pneumonia—Histiocytes—Sudden infant death—Lymphocytes—Monoclonal antibodies.

The lungs of infants with viral or other kinds of interstitial pneumonia may show relatively little inflammatory response due to immaturity of the immune system. Conversely, substantial inflammation may be present, but is not detected due to the highly cellular structure of the infant lung. In this report of a 15-week-old infant girl whose cause of death was originally diagnosed as sudden infant death (SID) syndrome, the finding of both an intraalveolar histiocytic desquamation and a lymphocytic interstitial infiltration afforded convincing evidence that a desquamative interstitial pneumonia (DIP) was the underlying cause of death.

## CASE REPORT

This 15-week-old black infant girl was born at home prematurely (33-week gestational age) to a 26-year-old mother and 21-year-old father. She was transferred to a hospital for 3 weeks and received gentamycin and ampicillin for 3 days. She had a history of exposure to *Candida* in the hospital, but blood and stool cultures showed no growth. Following discharge, there were no complications or new illnesses. The infant was examined by a private physician 2 weeks prior to her death, and her behavior was said to be normal. Information about the terminal episode is scanty. The infant was fed at 4:00 a.m. and presumably was behaving somewhat abnormally since, at the father's urging, she was placed in the parent's bed, to sleep between them. Neither parent recalled any specific signs or symptoms of illness. Three hours after the infant had been fed, the parents awakened and found her to be unresponsive. Ambulance attendants arrived moments later and found her to be pulseless and apneic. Immediate resuscitation was started and was continued during transport to the hospital. On arrival at the hospital, the infant's pupils were fixed

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APPENDIX I

ABSTRACTS AND PRESENTATIONS

Presented at the Air Waste Management
Association Meeting, June, 1988

# THE ROLE OF AIR POLLUTION IN THE DEPLETION OF HEALTH RESERVES

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Quantitative image analysis of the lungs of mice exposed to ambient levels of ozone and/or nitrogen dioxide has shown alterations of the cellular ecology that persisted 32 weeks postexposure, e.g. Type 2 cell hyperplasia and hypertrophy, increased alveolar wall area, and increased elastic tissue. The results, extrapolated to the human well population, suggest that air pollution may be accelerating the decremental loss of lung structure and function that occurs in all adults. Even a relatively small increment in the rate of irreversible lung damage may over the long term impact seriously on health by depleting lung reserves below a tolerable level. Pertinently, the majority of lungs from 64 "healthy" 15-25 year old adults (coroner cases) showed substantial depletion of lung reserves. We may have examined an unusual subpopulation, but it is possible we are observing "early" adverse effects of the environment. Of further pertinence, mice exposed to ambient air pollution in Los Angeles showed microecologic alterations when compared to those in the less polluted air of Santa Barbara. Conservation of reserves provides resistance to stress and disease, and the opportunity for a high quality as well as full lifespan.

Supported in part by the California Air Resources Board (A6-202-33), and by the Hastings Foundation

Presented at the Air Waste Management
Association Meeting, March, 1990

# CENTRIACINAR REGION (CAR) DISEASE IN THE LUNGS OF YOUNG ADULTS
## A PRELIMINARY REPORT

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Our ongoing study is correlating lung lesions, incidentally found in 15 to 25 yr old young adults, with air quality at the place of residence. From Coroner cases (vehicular deaths and homicides), lungs from 89 individuals were inflated with 4% buffered formalin at 25 cm water pressure for a minimum of 48 hrs. Whole lung slices provided five representative sections of the lower lobe, and these were quantitated (0-10 severity; 0-10 extent) without prior demographic data. We report an unexpected frequency (72/89; 81%) and severity of one type of CAR lesion that we have identified as a Desquamative Bronchioloalveolitis (DBA) and which is known to be produced by diverse noxious agents. The minimal to slight DBA lesion (28%) was the filling of one or more proximal acinic lumina with macrophages that usually contained a brown pigment. In the severe lesions (26/89; 29%) most of the CAR lumina were heavily involved, and 65% also had local thickening of bronchiolar and alveolar walls due to macrophage infiltration and, to a lesser extent, interstitial fibrosis. Moreover, we found a chronic inflammatory cell infiltration of the walls and "tips" of respiratory bronchioles in 69% of the DBA lesions. Moderate disease involved 24%. Hyperplastic nodules were rare. Intracellular and free pigment associated with DBA was occasionally iron positive, and there was a spectrum of color from a pale yellow brown to black, with some blurring of distinctions from "anthracotic" and acid hematin pigments. Relatively small numbers of birefringent silica/silicate particles were found, with a few exceptions. The findings are conservative in that CAR lesions in general are more frequent in the upper lobe (which we used to study emphysema and, in part, the uninflated lung), and we have not included CAR lesions other than DBA.

The high incidence of DBA may be biased by the predominance of a central Los Angeles residence, as suggested by the limited data presently available. The smoking incidence, including marijuana, may be high and socioeconomic factors are probably involved. Poor hygiene as well as poor nutrition may predispose to viral infections, dust diseases of the lung, and other agents known to injure the CAR preferentially. Although lesions of the CAR may occupy only 15% of lung volume, that volume can impact on essentially all of air flow, making CAR lesions important discriminants for inventories of lung reserve. A loss of reserves can substantially increase susceptibility to disease in general, and an inordinate rate of loss over the long term can lead to emphysema and other destructive lung diseases. Since CAR lesions have been produced by exposing animals to ambient levels of ozone, and since there is mounting evidence that community air pollution alters lung function and structure of well populations, there is little question that exceedences of air quality standards throughout the country have some impact on lung reserve depletion. Unanswered is the main question we raise -- is air pollution in Los Angeles and elsewhere greatly amplifying injury to the lung and thereby contributing to a presently unappreciated, widespread, and inordinately high rate of lung reserve depletion.

Supported in part by California Air Resources Board Contract A6-202-33, and by the Hastings Foundation.

ABSTRACTS AND PRESENTATIONS

1. Sherwin RP, Richters V, Richters A.
   The role of air pollution in the depletion of health reserves.
   Presented to the EPA, Triangle Park, North Carolina, September 12, 1988.

2. Sherwin RP, Richters V, Richters A.
   The role of air pollution in the depletion of health reserves.
   Presented at the JAPCA meeting, Anaheim, California, June 20, 1988.

3. Lung Injury Workshop.
   Part I - Los Angeles, California, August 2, 1989.
   Part II - Durham, North Carolina, September 16-17, 1989.

4. Sherwin RP.
   An on-going autopsy study.
   Presented at the Collogium on Epidemiology and Air Pollution, Sponsored by the California Air Resources Board and US Environmental Protection
   Agency, December 12-13, 1989.

5. Sherwin RP, Richters V.
   Centriacinar region (CAR) disease in the lungs of young adults. Preliminary report.
   Presented at the Air Waste Management Association Meeting on March 21, 1990, City of Industry, California.

6. Sherwin RP. Centri-acinar region disease in youths 15-25 living in Los Angeles County: A preliminary report.
   Presented at The Trudeau Society of Los Angeles on April 24, 1990.